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2017 APS Conference
Cardiovascular Aging: New Frontiers and Old Friends
August 11-14, 2017, Westminster, Colorado

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Acknowledgements

The Conference Organizers and The American Physiological Society gratefully recognize the generous financial support from the following:
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GENERAL ANNOUNCEMENTS

• An Opening Reception will be held Friday, August 11 at 7:00 PM – 8:00 PM on the South Courtyard featuring an open bar and a variety of locally-sourced appetizers. In case of inclement weather, the reception will be held in the Ballroom Foyer.

TRAINEE TRAVEL AWARD FINALISTS

• Six Travel Award Finalists were selected by the Conference Organizing Committee. Judges will attend presentations and score presentations based on oral presentation. Winner(s) will be announced during the Closing Remarks session on Monday, August 14 at 11:30 AM. Oral presentation schedule is listed below. Best of luck to all!

<table>
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<tr>
<th>Finalist Name</th>
<th>Presentation Date</th>
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<td>Ait Aissa, Karima</td>
<td>Friday, August 11, 2017</td>
<td>6:15 PM – 6:30 PM</td>
<td>3.1 (oral)</td>
<td>Role of DAMPs in Development of Microvascular Dysfunction in Human Coronary Artery Disease</td>
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<td>De Boer, Martine</td>
<td>Sunday, August 13, 2017</td>
<td>3:30 PM – 3:45 PM</td>
<td>12.4 (oral)</td>
<td>DNA-repair in Cardiomyocytes is Critical for Maintaining Cardiac Function</td>
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<td>Racine, Matthew</td>
<td>Friday, August 11, 2017</td>
<td>6:30 PM – 6:45 PM</td>
<td>3.2 (oral)</td>
<td>Mechanisms of Impaired Deoxygenation-induced Red Blood Cell ATP Release in Older Adults: Roles of Cell Deformability and cAMP</td>
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<td>Pedrinolla, Anna</td>
<td>Sunday, August 13, 2017</td>
<td>12:00 PM – 12:15 PM</td>
<td>11.5 (oral)</td>
<td>Progression of Alzheimer's Disease: The Role of Nitric Oxide Bioavailability in Cerebral and Peripheral Circulation</td>
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<td>Rossman, Matthew J.</td>
<td>Monday, August 14, 2017</td>
<td>11:00 AM – 11:15 AM</td>
<td>14.5 (oral)</td>
<td>MitoQ Supplementation Improves Vascular Endothelial Function in Health Late Middle-aged and Older Adults</td>
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<td>Shin, Song Yi</td>
<td>Friday, August 11, 2017</td>
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<td>3.3 (oral)</td>
<td>Effect of Intraluminal Pressure on Vascular Smooth Muscle Contractility in Aged Skeletal Muscle Resistance Arteries</td>
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**Location:**

**Onsite Registration Hours:**
Fri., August 11 ............................. 3:00 PM – 8:00 PM
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Sun., August 13 ............................ 7:30 AM – 5:30 PM
Mon., August 14 ........................ 7:30 AM – 11:30 AM

**Student Registration:**
Any student member or regularly matriculated student working toward a degree in one of the biomedical sciences is eligible to register at the student fee. Nonmember postdoctoral fellows, hospital residents and interns, and laboratory technicians do not qualify as students. Non-member students who register onsite must provide a valid university student ID card. APS student members should present their current APS membership card indicating their student category status.

**Postdoctoral Registration:**
Any person who has received a Ph.D. degree in physiology or related field, within five years of the conference start date, as attested to by the department head is eligible to register at the postdoctoral fee. A statement signed by the department head must accompany the registration form and remittance when registering.

**Included in your Registration:**
Your registration to this conference includes entry into all scientific sessions, program book, opening reception, and poster sessions. **Registration is nontransferable.** You must pay the entire fee regardless of the number of sessions/events you attend. Guests of attendees are not permitted in the scientific sessions, opening reception or conference breaks and social events.

**Press Registration:**
Press badges will be issued at the Conference Registration desk to members of the working press and freelance writers bearing a letter of assignment from an editor. Representatives of allied fields (public relations, public affairs, etc.) must register as nonmembers.

**Photograph/Video Recording:**
Photo or video capture of any scientific presentation in whole or part is expressly prohibited. Recording or taking photography of another person without their explicit permission is prohibited.

**Code of Conduct:**
APS is committed to providing a safe, productive and welcoming environment for all conference participants and staff. All participants including, but not limited to, attendees, speakers, volunteers, APS staff, hotel staff, service providers and others are expected to abide by the APS Conference Code of Conduct which maintains that all individuals should: be treated with respect and consideration, valuing a diversity of views and opinions; be considerate, respectful and collaborative; communicate openly and with respect, critiquing ideas rather than individuals; avoid personal attacks; be mindful of your surroundings and fellow participants; and, be respectful of the rules APS and the conference venue. Contact the APS staff at the Conference Registration Desk if you notice a dangerous situation, someone in distress, or violations of this Code of Conduct.

**Program Objective:**
Aging is the number one risk factor of cardiovascular disease (CVD). Recent advances in the understanding of cellular aging have taught us much about how arterial aging and its mechanisms contribute to the development of CVD. Mitochondria and free radical signaling, immune cell responses and cellular inflammation are just a few of the contributing factors. Novel developments in this field not only have implications for the overall health and well-being of older adults but also for age-associated disease such as atherosclerosis, hypertension, and metabolic syndrome.

The sessions will discuss the implications of aging vascular systems in a host of different physiological systems, organs and tissues. These sessions will emphasize the translation of cell and molecular observations to ex vivo and intact mammalian systems. Topics include age-related arterial disease states such as: atherosclerosis, hypertension, heart failure, as well as age-related tissue and systems dysfunction that are not typically thought to be influenced by vascular function such as, cancer, metabolic syndrome and autoimmune diseases.

This conference will draw physiologists and investigators from other translational fields of study that are interested in cardiovascular function and disease. Much of the information to be presented was discovered and matured after these investigators left formal training, or was not the focus of their education, but has become increasingly important in recent years. These investigators will find this conference attractive and informative.
FRIDAY, AUGUST 11, 2017

Opening Remarks

1.0 WELCOME AND OPENING COMMENTS
Fri., 5:00-5:10 PM, Westminster II

Lecture

2.0 STRATEGIES FOR OPTIMAL CARDIOVASCULAR AGING
Fri., 5:10-6:15 PM, Westminster II
Douglas Seals, Univ. of Colorado, Boulder.

Oral Presentations

3.0 TRAINEE AWARD COMPETITION
Fri., 6:15-7:00 PM, Westminster I

SATURDAY, AUGUST 12, 2017

Symposium

4.0 COUNTERMEASURES TO CARDIOVASCULAR AGING
Sat., 8:00-10:45 AM, Westminster II
Chairs: Lisa Lesniewski, Univ. of Utah. Amanda Jo LeBlanc, Univ. of Louisville.

8:00 AM 4.1 Rapamycin and Elamipretide (SS-31): Interventions to Reverse Cardiac Aging by Enhancing Mitochondrial Function. Peter Rabinovitch, Univ. of Washington.

8:30 AM 4.2 Late-life Exercise Training Reverses Age-related Microvascular Dysfunction: A Role for Adiponectin. Judy Muller-Delp, Florida State Univ.

9:00 AM 4.3 Modulatory Influences of Sex Hormones on Vascular Aging. Kerrie Moreau, Univ. of Colorado, Aurora.

9:30 AM Break

10:00 AM 4.4 Intravenous Adipose-derived Cell Therapy Improves Cardiovascular Performance in Aged Rats. Amanda Jo LeBlanc, Univ. of Louisville

10:30 AM 4.5 Cardiac Myosin Binding Proetien-C Phosphorylation Improves Longevity and Preserves Heart Function in Aging Hearts. Paola Rosas, Texas A&M Univ. (13.3)

Posters

5.0 POSTER SESSION I
Sat., 10:45 AM-12:00 Noon, Westminster I

1 5.1 MitoQ Supplementation Improves Vascular Endothelial Function in Health Late Middle-aged and Older Adults. Matthew J. Rosman, Jessica R. Santos-Parker, Lauren M. Cuevas, Chelsea A.C. Steward, Nina Z. Bispham, Hannah L. Rosenberg, Rachel A. Gioscia-Ryan, Kayla A. Woodward, Michel Chonchol, Michael P. Murphy, Douglas R. Seals, Univ. of Colorado, Boulder.
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<th>Progression of Alzheimer's Disease: The Role of Nitric Oxide Bioavailability in Cerebral and Peripheral Circulation. Anna Pedrinolla, Massimo Venturelli, Cristina Fonte, Ilaria Boscolo Galazzo, Lucia Crispoltoni, Maria Vittoria Benetti, Anna Stabile, Annalisa Brugnera, Alessandra Pistilli, Mario Rende, Francesca Benedetta Pizzini, Nicola Smania, Federico Schena. Univ. of Verona, Italy.</th>
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<td>Acute and Chronic Effects of e-Cigarette Vapor Exposure on Vascular Function: New Friend or Old Foe? Mark Olfert, Stuart Clayton, Evan DeVallance, Kayla Branyan, Chris Pitzer, Matt Breit, Hannah Hoskinson, Kyle Mandler, Brett Erdreich, Powsiri Klinkchachorn, Paul Chantler. West Virginia Univ.</td>
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<td>Contradictory Indicators of Arterial Stiffening During Long-duration Spaceflight. Richard Hughson, Philippe Arbeille, Kevin Shoemaker, Danielle Greaves. Univ. of Waterloo Res. Inst. for Aging., Canada.</td>
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<td>5.5</td>
<td>Leukocyte Telomere Length and Arterial Stiffening Across the Stages of the Menopause Transition. Kerry Hildreth, Wendy Kohrt, Kerrie Moreau. Univ. of Colorado, Aurora.</td>
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<td>12</td>
<td>5.12</td>
<td>Prehypertension Accelerates Vascular Aging Across the Menopausal Transition inbb Healthy Women. Elizabeth Crow BA, Kerry Hildreth, Cemal Ozemek, Teresa Witten, Kerrie Moreau. Univ. of Colorado, Aurora.</td>
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<td>Oxidative Stress Contributes to Age-associated Reduced Left Ventricular Diastolic Function in Men. Shauna Runcheey, Kerry Hildreth, Amy Keller, Teresa Witten, Elizabeth Crow, Brian Stauffer, Wendy Kohrt, Robert Schwartz, Kerrie Moreau. Univ. of Colorado, Aurora.</td>
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<td>16</td>
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<td>The Impact of Menopausal Stage and Aerobic Fitness on Endothelial Function and Responses to Acute Exercise. Corinna Serviente, Sarah Witkowski. Univ. of Massachusetts, Amherst.</td>
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Symposium
6.0 NOVEL MECHANISMS OF BLOOD FLOW CONTROL AND MICROVASCULAR FUNCTION WITH AGE
Sat., 1:30-4:15 PM, Westminster II

Chair: Frank Dinенно, Colorado State Univ.

1:30 PM 6.1 Skeletal Muscle Oxygen Transport During Exercise: Effects of Aging and Heart Failure. David Poole. Kansas State Univ.

2:00 PM 6.2 Regulation of Skeletal Muscle Blood Flow During Exercise in Aging Humans. Frank Dinенно. Colorado State Univ.

2:30 PM 6.3 The Impact of Age and Hypertension on Cutaneous Microvascular Function. Lacy Alexander. Penn State Univ.

3:00 PM Break

3:30 PM 6.4 Microvascular Adaptations During Aging: Opportunities for New Models and Discoveries. Walter Murfee. Tulane Univ.

4:00 PM 6.5 Effect of L-Citrulline on Exercise Blood Flow in Older Women and Men. Joaquin U. Gonzales. Texas Tech. Univ. (5.7)

Career Workshop
7.0 NAVIGATING THE INS AND OUTS OF GRADUATE SCHOOL
Sat., 4:30-5:30 PM, Westminster II

Chair: Daniel Craighead, Penn State Univ.

Symposium
8.0 NOVEL IMPLICATIONS FOR BLOOD FLOW AND VASCULAR DYSFUNCTION IN NON-CARDIOVASCULAR RELATED DISEASES
Sat., 6:00-7:15 PM, Westminster II

Chair: Judy Muller-Delp, Florida State Univ.

6:00 PM 8.1 Implications for Blood Flow in Prostate Cancer: Tumor/Systemic Interactions, Central and Peripheral Cardiovascular Function. Brad Behnke. Kansas State Univ.

6:30 PM 8.2 Endothelial Dysfunction in the Adipose: A Key Regulator of Age Related Metabolic Dysfunction? Lisa Lesniewski. Univ. of Utah.

7:00 PM 8.3 Aging Enhances Atrial Fibrillation Inducibility in Atherosclerotic Hosts. Dan Tyrrell. Univ. of Michigan. (13.14)
Tutorial

9.0 HOW MUCH DO YOU KNOW ABOUT AJP-HEART AND CIRCULATORY PHYSIOLOGY? GET THE GUIDED TOUR
Sat., 7:30-8:30 PM, Westminster II
Chair: Kara Hansell Keehan, American Physiological Society.

SUNDAY, AUGUST 13, 2017

Lecture

10.0 BLOOD PRESSURE TARGETS FOR OLDER ADULTS: IMPLICATIONS FOR COGNITIVE AND CARDIOVASCULAR DISEASE ENDPOINTS
Sun., 8:30-9:20 AM, Westminster II
Mark Supiano. Univ. of Utah.

Symposium

11.0 NOVEL MECHANISMS UNDERLYING VASCULAR IMPAIRMENTS IN THE AGING BRAIN
Sun., 9:30 AM-12:15 PM, Westminster II
Chair: Prasad Katakam, Tulane Univ.
9:30 AM 11.1 Pulse Pressure in the Aging Brain. Eric Thorin. Univ. of Montreal, Canada.
10:00 AM 11.2 Aging Increased Blood Pressure and Alters the Biomechanical Properties of the Posterior Cerebral Arteries and the Parenchymal Arterioles. Anne Dorrance. Michigan State Univ.
10:30 AM 11.3 Human Cerebral Artery Function and Aging. Jill Barnes. Univ. of Wisconsin, Madison.
11:00 AM Break
11:30 AM 11.4 Role of Endothelial nNOS in Age-related Microvascular Impairments. Prasad Katakam. Tulane Univ.
12:00 Noon 11.5 Progression of Alzheimer's Disease: The Role of Nitric Oxide Bioavailability in Cerebral and Periphreal Circulation. Anna Pedrinolla. Univ. of Verona, Italy. (5.2)

Symposium

12.0 CELLULAR SENESCENCE AND GENOMIC INSTABILITY: IMPLICATIONS FOR CARDIOVASCULAR DISEASE
Sun., 1:30-4:00 PM, Westminster II
Chair: Anthony Donato, Univ. of Utah.
1:30 PM 12.1 Cellular Senescence and Senolytic Agents in Age-related Dysfunction and Chronic Diseases. James Kirkland. Mayo Clinic.
2:10 PM 12.2 Age-related Arterial ALU Element Instability and Survival in Melanoma Patients. R. Garrett Morgan. Univ. of Utah.
2:35 PM  12.4 DNA-repair in Cardiomyocytes is Critical for Maintaining Cardiac Function. **Martine de Boer.** *Erasmus MC, Rotterdam, The Netherlands.* (13.5)

3:00 PM  Break

3:20 PM  12.3 Vascular Telomere Dysfunction: Association with Aging and Functional Implications. **Ashley Walker.** *Univ. of Utah.*

4:00 PM  12.5 Estrogen Treatment and Cellular Senescence on Proteostasis Maintenance in Endothelial Cells. **Hyun Tae Hwang.** *Univ. of California, Davis.* (13.18)

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**Posters**

13.0  **POSTER SESSION II**

Sun., 4:00-5:30 PM, Westminster I

19  13.1 Myofilament and Biochemical Responses of the Right Ventricle to Hypoxia-related Cardiac Dysfunction in Aging. **Danielle Bruns, Mark Jeong, Peter Buttrick, Lori Walker.** *Univ. of Colorado, Denver.*

20  13.2 Aging-associated Upregulation of Cardiac β3-adrenergic Signaling is an Important Cause of Cardiac Aging. **Heng-Jie Cheng, Peng Zhou, Zhi Zhang, Satoshi Masutani, Dalane Kitzman, Michael Callahan, ChePing Cheng.** *Wake Forest Univ.*

21  13.3 Cardiac Myosin Binding Protein-C Phosphorylation Improves Longevity and Preserves Heart Function in Aging Hearts. **Paola Rosas, Carl Tong.** *Texas A&M Univ.*

22  13.4 Early Cell-cell Coupling Impairs Transplanted Stem Cell Retention and Efficacy in the Ischemic Cardiomyocyte and Murine Heart. **Santipongse Chatchavalvanich, David Geenen.** *Mahidol Univ., Bangkok.*

23  13.5 DNA-repair in Cardiomyocytes is Critical for Maintaining Cardiac Function. **Martine de Boer, Marion G.J. de Kleijnen, Yanti Octavia, Bibi S. van Thiel, Yanto Ridwan, Maaike te Lintel Hekkert, Ingrid van der Pluijm, Jeroen Essers, Jan H. Hoeijmakers, Dirk J. Duncker.** *Erasmus MC, Rotterdam, The Netherlands.*

24  13.6 The Effects of Aging on Pathologic Left Venticular Remodeling and Dysfunction Depend Critically on the Underlying Pathology. **Martine de Boer, Elza D. van Deel, Nicky M. Boontje, Marion G.J. de Kleijnen, Jolanda van der Velden, Jan H. Hoeijmakers, Dirk J. Duncker.** *Erasmus MC, Rotterdam, The Netherlands.*

25  13.7 Advance Age and Circulating miR423 are Independent Predictors of Postoperative Atrial Fibrillation. **Farhan Rizvi, Susan Olet, Stacie Edwards, Mahek Mirza, Larisa Emelyanova, Gracious R. Ross, Indrajit Choudhuri, David Kress, Jasbir Sra, A. Jamil Tajik, Arshad Jahangir.** *Aurora Health Care, Milwaukee.*

26  13.8 Store-operated Ca2+ Influx in Human Ventricular Fibroblasts Increases by Age. **Gracious R. Ross, Stacie Edwards, Sean D. Ryan, Farhan Rizvi, Paul Werner, A. Jamil Tajik, Arshad Jahangir.** *Aurora Health Care, Milwaukee.*

27  13.9 Cardiac Troponin T and Endothelial Cell Dysfunction in Aging and Alzheimer's Disease. **Juan Dong, Xin Feng, Fei Xing, Tao Ma, Tan Zhang.** *Wake Forest Univ.*

28  13.10 SIRT-1 Overexpression Mitigates Large Artery Stiffening with Advancing Age. **Daniel R. Machin, Yauling Auduong, Grant D. Henson, Lisa A. Lesniewski, Anthony J. Donato.** *Univ. of Utah.*


13.18  Estrogen Treatment and Cellular Senescence on Proteostasis Maintenance in Endothelial Cells. Hyun Tae Hwang, Anne Knowlton. Univ. of California, Davis.


13.20  Altered Mitochondrial Responses to Nitric Oxide Synthase Inhibitors in Isolated Cardiac Mitochondria from Young and Aged Rats. Siva Sakamuri, Jared Sperling, Monica Dholakia, Venkata Sure, Prasad Katakam. Tulane Univ. Sch. of Med.

13.21  Acute Iysyl Oxidase Inhibition Augments Endothelium-dependent Vasodilation in Young, but not Middle-aged, Men and Women. Daniel Craighead, Lakshmi Santhanam, Lacy Alexander. Penn State Univ.


**Symposium**

**14.0** MITOCHONDRIA: THE EPICENTER OF AGING RELATED CARDIOVASCULAR DEFECTS  
Mon., 8:30-11:30 AM, Westminster I.

Chair: Andreas Beyer, Med. Coll. of Wisconsin, Milwaukee.

- **9:00 AM** 14.2 Oxygen Metabolism, Tissue Responses to Hypoxia, Oxidative Stress, and Molecular Mechanisms of Oxygen Sensing by Mitochondria. Paul Schumacker. Northwestern Univ.
- **9:30 AM** 14.3 Metabolic Regulation of Age-related Mitochondria Defects. Changhan David Lee. Univ. of Southern California.

**10:00 AM** Break

- **11:00 AM** 14.5 MitoQ Supplementation Improves Vascular Endothelial Function in Health Late Middle-aged and Older Adults. Matthew J. Rossman. Univ. of Colorado, Boulder. (5.1)
- **11:15 AM** 14.6 Reduced Glycolysis and Increased Oxygen Consumption with Aging in Endothelial Cells. Venkateswara R. Gogulamudi. Univ. of Utah. (13.19)

**Closing Remarks**

**15.0** AGING AND CARDIOVASCULAR DISEASES: WHAT IS NOW, WHAT IS NEXT?  
Mon., 11:30-11:45 AM, Westminster I.

Chair: Anthony Donato, Univ. of Utah.
Posters

LB  LATE BREAKING POSTERS
   Sun., 4:00-5:30 PM, Westminster I

Board #


48  LB003 Higher Plasma Concentrations of the Gut-Derived Metabolic Trimethylamine N-Oxide is Correlated with Impaired Arterial and Cognitive Function in Young and Older Healthy Adults. Vienna E. Brunt, Rachael A. Gioscia-Ryan, Kevin P. Davy, Andrew P. Neilson, Douglas R. Seals. Univ. of Colorado, Boulder and Virginia Polytech. Inst. and State Univ., Blacksburg, VA.


ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

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**2.0 LECTURE**

**2.1 STRATEGIES FOR OPTIMAL CARDIOVASCULAR AGING**

*Douglas Seals*¹

¹Integrative Physiology, University of Colorado Boulder, 354 UCB, Boulder, CO, 80309

Cardiovascular diseases (CVD) remain the leading causes of morbidity and mortality in the U.S., and aging is by far the greatest risk factor for CVD. Much of the increase in CVD risk with aging is driven by adverse changes to arteries, most prominently large elastic artery stiffening and endothelial dysfunction, which, in turn, induce secondary detrimental effects on the heart and systemic circulation. Arterial dysfunction also contributes to many other common conditions of aging including cognitive/motor disorders and metabolic and kidney diseases. Altered vasoactive signaling featuring reduced nitric oxide bioavailability and modifications in the expression and architecture of structural proteins in the arterial wall are key characteristics of arterial aging. Two mechanistic Old Friends responsible for these changes are chronic oxidative stress and low-grade inflammation (inflammaging). As such, identifying the upstream processes that contribute to oxidative stress and inflammation is one of the New Frontiers of arterial aging research. Presently there is evidence for mitochondrial dysfunction, impaired autophagy/mitophagy, dysregulated energy-sensing pathways and sex hormone deficiency playing important roles. However, other fundamental mechanisms of biological aging, including cellular senescence, reduced stress resistance, genomic instability, telomere attrition, reduced proteostasis, stem cell dysfunction and/or epigenetic modifications, along with gut dysbiosis, also may contribute. Strategies for which there is extensive experimental evidence of benefit may be considered preventive and/or therapeutic Old Friends for arterial aging, and include healthy lifestyle practices such as regular aerobic exercise, limiting energy intake, and healthy diet composition. These strategies act to maintain arterial function and health with aging by favorably modulating one or more of the above processes to suppress oxidative stress and inflammation. Several novel strategies represent New Frontiers, but presently lack evidence for efficacy, particularly in humans. These include alternative exercise training regimens (e.g., high-intensity interval training); behavior (intermittent fasting) or pharmacological (sirtuin-activating and NAD⁺-boosting compounds) based chronic energy restriction-mimicking paradigms; healthy diet composition-inspired nutraceuticals (supplements, functional foods); and environmental stress-leveraged interventions (e.g., heat therapy).

**4.0 SYMPOSIUM: COUNTERMEASURES TO CARDIOVASCULAR AGING**

**4.1 RAPAMYCIN AND ELAMIPRETIDE (SS-31): INTERVENTIONS TO REVERSE CARDIAC AGING BY ENHANING MITOCHONDRIAL FUNCTION**

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Aging is associated with significant declines in skeletal and cardiac muscle function and a higher incidence of cardiovascular disease. Even in healthy individuals, aging results in increased prevalence of sarcopenia, left ventricular hypertrophy, impaired diastolic function and reduced myocardial performance. These same changes are seen in aging mice, making them a useful model for studies of muscle healthspan. We were able to show that transgenic mice expressing mitochondrial catalase (mCAT), displayed delayed cardiac aging. Subsequently, we have been interested in whether shorter term pharmacologic treatments might be able to reverse the functional deficits of skeletal and cardiac muscle aging in old mice. The mitochondrial protective SS-31 peptide (elamipretide) offers similar benefits as mCAT in models of pressure overload-induced cardiac hypertrophy and failure. This agent has recently been shown to bind to cardiolipin and improve the electron carrying function of cytochrome c, while reducing its peroxidase activity. We have now found that 24 month old mice receiving SS-31 for 8 weeks have improved skeletal muscle energetics, function and endurance, enhanced cardiac diastolic function, improved myocardial performance, reduced cardiac hypertrophy and increased exercise endurance. The cardiac improvements are persistent after removal of the drug, with a half-time of approximately 2 weeks. Continuing this theme, we found that 8 week rapamycin treatment can also reverse established cardiac aging, inducing proteomic and metabolic remodeling that improves mitochondrial energy metabolism. Interestingly, rejuvenation of cardiac function by 8 week rapamycin treatment is persistent for longer than 8 weeks after the drug treatment is withdrawn. Results with both rapamycin and SS-31 indicate that short-term treatments can enhance mitochondrial function and reverse muscle aging phenotypes in old mice and that these benefits can be long-lasting. Thus, interventions that target mitochondrial function can have a high translational potential, with late-life treatments conferring healthspan improvements with persistent benefits. Support: NIH grants P01AG001751, P30 AG013280, R01 AG038550.

**4.2 LATE-LIFE EXERCISE TRAINING REVERSES AGE-RELATED MICROVASCULAR DYSFUNCTION: A ROLE FOR ADIPONECtin**

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Coronary microvascular function and blood flow responses to acute exercise are impaired in the aged heart, but can be restored by exercise training. Age impairs myogenic responsiveness of coronary arterioles; however, even at an advanced age, exercise training restores myogenic responses of coronary arterioles. Adiponectin has also been implicated
in maintenance of optimal cardiovascular function due to 1) enhancement of endothelial function and stimulation of angiogenesis, and 2) regulation of smooth muscle differentiation and prevention of atherosclerosis. We assessed contractile function and vascular smooth muscle phenotypic changes, as well as adiponectin signaling in coronary arterioles from young and old Fischer 344 rats that either underwent 10 weeks of treadmill exercise training or remained sedentary. Contractile function was impaired in coronary arterioles from aged rats, and vascular smooth muscle shifted from a differentiated, contractile phenotype to a secretory phenotype with associated hypertrophy of smooth muscle in the arteriolar wall. Circulating adiponectin and arteriolar expression of downstream signaling molecules, adenosine monophosphate-activated kinase (AMPK) and smooth muscle myosin heavy chain, were decreased in aged rats, whereas expression of the synthetic protein, ribosomal protein S6 (rpS6) and phosphorylated rpS6 was increased. Exercise training improved contractile function in coronary arterioles from old rats and restored a contractile phenotype to arteriolar smooth muscle. Exercise training increased circulating adiponectin, restored arteriolar expression of AMPK and smooth muscle myosin heavy chain, and decreased the level of rpS6 and phosphorylated rpS6 in coronary arterioles from old rats. Thus, age-induced contractile dysfunction and emergence of a secretory smooth muscle phenotype in coronary arterioles are reversed by late-life exercise training, possibly through increased adiponectin signaling.

4.3 MODULATORY INFLUENCES OF SEX HORMONES ON VASCULAR AGING
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Vascular aging, featuring endothelial dysfunction, is a major risk factor for developing age-associated cardiovascular diseases (CVD). In women, the decline in endothelial function is attenuated until menopause, whereafter the rate of decline accelerates to match that seen in men. Sex differences in the decline in endothelial function have been attributed to changes in gonadal hormones with aging. In women, we have demonstrated a progressive impairment in endothelial function across the stages of the menopause transition, related in part, to declining estradiol (E2) levels. Additionally, we and others demonstrate that endothelial function can be improved with E2 treatment in postmenopausal women. In contrast to women, little is known about the impact of declining testosterone (T) levels on endothelial function in men, but some evidence suggests greater endothelial dysfunction in men with low T compared to men with higher T. Our research employs short-term gonadal suppression models to manipulate sex hormones in an acute and reversible manner to distinguish the independent mechanisms of action of gonadal hormones from other factors (e.g., adiposity) that may influence vascular function during more chronic sex hormone withdrawal. Our preliminary observations demonstrate that short-term lowering of E2 and T in women and men, respectively, impairs endothelial function, and that oxidative stress is a key mechanism underlying this impairment. The underlying causes of the oxidative stress and endothelial dysfunction are unknown, but may be related to impairments in endothelial nitric oxide synthase and mitochondrial function. Further investigations into the defects that intersect vascular and gonadal aging will inform effective sex-specific intervention strategies to preserve vascular health and prevent CVD.

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4.4 INTRAVENOUS ADIPOSE-DERIVED CELL THERAPY IMPROVES CARDIOVASCULAR PERFORMANCE IN AGED RATS
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Over 50% of adult women presenting with symptoms of ischemic heart disease have “clear” coronary artery angiograms. Additional testing indicates coronary microvascular dysfunction contributes to the coronary perfusion deficits in these women. Current therapies for this condition, called microvascular angina, are relatively ineffective. Our previous research demonstrated that tissue-resident macrophages within the therapeutic cell preparation derived from the stromal vascular fraction (SVF) of adipose tissue improved peripheral small artery function. Delivered IV, these SVF-derived macrophages migrate to the walls of small vessels and reset vasomotor tone. Therefore, we hypothesized that IV delivery of SVF cells could reverse coronary microvascular dysfunction. Using the aged female Fisher-344 rat (22 mos. of age) as a model of coronary microvascular dysfunction without coronary artery involvement, combined with high-resolution ultrasound and indwelling chronic telemetry, we evaluated cardiac function and coronary flow reserve (CFR) in aged animals receiving fluorescently tagged GFP+ SVF cells from syngeneic young rats (6 x 106 cells/rat) via the tail vein at one-week and four-weeks post-injection. At the time of explant, the location of injected SVF cells was determined via confocal microscopy, and isolated coronary arteriole preparations were used to evaluate vasoreactivity. Injected GFP+ SVF cells had incorporated into the coronary vasculature one-week post-injection and remained there at 4 weeks. While coronary blood flow was improved in animals receiving the cell therapy, vasoreactivity of isolated arterioles to flow, pressure, bradykinin, and endothelin was unaffected. Measures of heart function such as maximal CO, percent HR increase, and LV EDD and EDV - which are all compromised in aged animals - were significantly improved in response to a dobutamine challenge compared to pre-SVF measurements. The cell
therapy did not lead to arrhythmias or increased mortality. Our findings indicate that IV-delivered adipose SVF cells disseminate to the aging heart and incorporate into the microvascular wall and perivascular spaces of the coronary vasculature. The presence of the therapeutic cells in the heart is associated with improved coronary perfusion and concomitant cardiac function. Funding: NIH ROI AG053585 (AJL) and P30 GM103507 (UoL), Jewish Heritage Fund for Excellence (AJL), Gheen’s Foundation (AJL).

5.0 POSTER SESSION I

5.1 MITOQ SUPPLEMENTATION IMPROVES VASCULAR ENDOTHELIAL FUNCTION IN HEALTHY LATE MIDDLE-AGED AND OLDER ADULTS

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Vascular endothelial dysfunction, as assessed by a decline in endothelium-dependent dilation (EDD), is a primary contributor to increased cardiovascular disease (CVD) risk with age. A key mechanism of reduced EDD with age is decreased bioavailability of the vasodilatory and vasoprotective molecule nitric oxide (NO) secondary to increased oxidative stress. Excessive reactive oxygen species production by mitochondria (mtROS) is emerging as a significant cause of vascular oxidative stress and reduced NO bioavailability with aging. Consistent with this concept, preclinical findings from our laboratory demonstrate that decreasing mtROS with the mitochondria-targeted antioxidant MitoQ restores NO-mediated EDD in old mice. The purpose of the current study was to translate our preclinical findings to humans by conducting a randomized, placebo-controlled, double-blind, crossover clinical trial to assess the efficacy of 6 weeks of oral MitoQ (20 mg/day) vs. placebo supplementation for improving EDD in healthy, late middle-aged and older adults (n=18, 60-79 yrs). EDD, measured by brachial artery flow-mediated dilation (FMDba), was increased by 48% with MitoQ vs. placebo (P<0.01), whereas endothelium-independent dilation (dilation with sublingual nitroglycerin) was unaffected (P>0.05). Additionally, MitoQ supplementation abolished tonic mtROS-mediated suppression of EDD, evaluated in a subset of subjects (n=7), as indicated by a 69% increase in FMDba with acute oral administration of 160 mg of MitoQ (P<0.05) under placebo conditions, but no change in FMDba with acute MitoQ (P>0.05) following 6 weeks of MitoQ supplementation. Participant characteristics were unaffected by MitoQ (all P>0.05). Collectively, these data suggest that MitoQ and other therapeutic strategies targeting mtROS may hold promise for treating vascular endothelial dysfunction and reducing CVD risk with aging.

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5.2 PROGRESSION OF ALZHEIMER’S DISEASE: THE ROLE OF NITRIC OXIDE BIOAVAILABILITY IN CEREBRAL AND PERIPHERAL CIRCULATION

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Background. In aging, cerebral and systemic circulation decline likewise to cognitive decline. Also, reduced availability of nitric oxide (NO) in both cerebral and peripheral blood vessels results in further alterations of circulation. Therefore, changes in circulation and NO bioavailability may contribute to the development of Alzheimer’s disease (AD). However, role of NO bioavailability in the control of extracranial blood flow, cerebral, and systemic circulation during AD progression have not been so far fully elucidated.

Methods. We assessed cortical circulation (partial volume correction) with arterial spin labeling (PVC-CBF), and measured internal carotid (CA), and femoral (FA) artery blood flow in young (YG), healthy old (OLD), patients with mild cognitive impairment (MCI), and in patients at 1st (AD1), 2nd (AD2), and 3rd (AD3) phase of AD. NO was determined via plasma NO metabolites (nitrite and nitrate concentrations), passive limb-movement (PLM) induced hyperemia was used to assess both NO bioavailability and systemic vascular function.

Results. Ninety-eight individuals (10 YG, 14 OLD, 19 MCI, 24 AD1, 20 AD2, and 11 AD3) were included in this study. PVC-CBF, CA, and FA blood flow were significantly (all p<0.05) reduced across the range from YG to OLD, MCI, AD1, AD2, AD3 subjects. Plasma level of nitrates was significantly reduced (p<0.05) among the 6 groups, with values of 67.8±4.2 µM in the YG, 58.1±5.1 µM in OLD, 51.1±3.0 µM in MCI, 45.1±3.7 µM in AD1, 39.2±3.7 µM in AD2, and 36.1±23.3 µM in AD3. Similarly, PLM was significantly decreased (p<0.05) in the 6 groups, with values of 439±59 ml&/d&ot;/min in YG, 298±38 ml&/d&ot;/min in OLD, 233±41 ml&/d&ot;/min in MCI, 202±25 ml&/d&ot;/min in AD1, 155±19 ml&/d&ot;/min in AD2, and 117±24 ml&/d&ot;/min in AD3. Significant correlations were retrieved between plasma nitrates and PLM, PVC-CBF, CA, as well as FA blood flow.
Conclusions. These results suggest that AD-related circulation impairment is progressive and not limited to the brain cortex, but it is likely the consequence of a systemic vascular dysfunction. The link between cardiovascular and the central nervous system degenerative processes during the progression of AD is likely related to the depletion of endogenous NO.

5.3 ACUTE AND CHRONIC EFFECTS OF E-CIGARETTE VAPOR EXPOSURE ON VASCULAR FUNCTION: NEW FRIEND OR OLD FOE?
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Background: Proponents for electronic cigarettes (E-cigs) claim they are a safe alternative to smoking tobacco-based cigarettes, however little is known about the acute and/or long-term effects of E-cig vapor exposure, particularly in the context of vascular (dys)function. We hypothesize that acute and chronic E-cig exposure would result in similar vascular dysfunction that has been observed with cigarette smoking.

Methods: Data were obtained from C57BL/6 female mice that were, either acutely (one 5 minute exposure, N=4) or chronically exposed (4 h/day, 5 d/wk for 8 months, N=6) to cappuccino flavored E-vapor (18 mg/ml nicotine). Intravital microscopy was used to assess arteriolar reactivity following acute exposure, and in-vivo Doppler ultrasonography was used to assess aortic stiffness (pulse wave velocity) at 3 times points (pre, during, post) with chronic exposure. After chronic exposure, the thoracic aorta was dissected, sectioned into rings and mounted onto an ex-vivo wire tension myograph system. Force transduction was used to measure the changes in aortic tension in response to vasodilatory compounds.

Results: Acute E-cigarette exposure resulted in no significant changes in baseline arteriolar vessel diameter; however 60 min post exposure arteriolar diameters were decreased by an average of 71% (p<0.001) and acetylcholine (ACh)-induced vasodilation was reduced by 9% (p<0.001) and 7% (p=0.05) 0 and 60 minutes, respectively. In chronically exposed mice, aortic stiffness increased 2.5 times greater in E-cig vs filtered-air exposed control mice (1.14±0.24 m/s 0.45±0.20 m/s, p<0.05, respectively). The maximal aortic relaxation achieved to methacholine was 90% in air exposed mice, and reduced to 70% in chronic E-cig exposed mice (P<0.05). No differences were noted in sodium nitroprusside dilation between the groups.

Conclusion: Our data provides the first evidence showing a single acute exposure has negative effects on in vivo vascular function, and that chronic exposure significantly accelerates age-associated increase in aortic stiffness, and significantly impairs aortic endothelial-dependent vasodilation. Endothelial-independent vasodilation was not alter with chronic E-cig exposure. These data indicate that E-cigs should not be considered safe, and that they induce significant deleterious effects on endothelial function in the central and peripheral vasculature.

5.4 CONTRADICTORY INDICATORS OF ARTERIAL STIFFENING DURING LONG-DURATION SPACEFLIGHT
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Removal of the normal head-to-foot gravitational vector during spaceflight alters several of the stimuli affecting arterial structure and function: there is a chronic relative hypertension in arteries above heart-level, elevation of hormones of the renin-angiotensin-aldosterone system, and marked reductions in daily physical activity with development of insulin resistance. Recently, we have studied changes in arterial properties in 17 astronauts in response to 6-months spaceflight. In the first study (Vascular) of 8 astronauts (4 women), we reported an increase in carotid artery stiffness that was similar to changes observed with aging ~20 years, and pulse wave transit time was reduced (Am J Physiol H628-38, 2016). In another recent study (Vessel Imaging), carotid artery intima-media thickness increased ~12% from pre-flight baseline (Aerosp Med Env Physiol 87: 449-53, 2016), and we found an increase from 0.48±0.07 mm to 0.55±0.1 mm (mean±SD, n=10, p=0.08) from pre- to post-flight. In a subsequent study of 9 male astronauts (BP Reg), we measured cardiac output by rebreathing (Q_RB) and finger arterial pulse contour analysis with Modelflow (Q_MF) in an upright seated position before flight and during flight. Q_RB increased 48% from pre-to inflight (4.76±0.67 to 7.00±1.40 L/min, p=0.001) while Q_MF was unchanged (6.60±1.95 to 5.91±1.16 L/min). Concurrent with the measures of Q_RB, brachial arterial pulse pressure was not different from pre- to inflight (63.3±10.5 to 57.2±15.9 mmHg); however, estimated arterial compliance (stroke volume/pulse pressure) increased from 1.24±0.21 to 2.23±0.90 mL/mmHg (p=0.004). Different methods in the two spaceflight studies resulted in different conclusions regarding changes in arterial stiffness. Local stiffness and wall thickness of the carotid artery increased comparing before to immediately after spaceflight. In contrast, overall arterial compliance increased inflight compared to pre-flight. Because Q_MF was unreliable with spaceflight, and we measured Q_RB only seated, there was not an opportunity to compare supine posture with spaceflight. We hypothesize that the inability of Q_MF to track change in cardiac output and the increase in arterial
Longitudinal studies are needed to determine the effects of the changing hormonal environment with menopause, independent from those of age, on telomeres.

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5.5 LEUKOCYTE TELOMERE LENGTH AND ARTERIAL STIFFENING ACROSS THE STAGES OF THE MENOPAUSE TRANSITION

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Background: Large artery stiffening is a consequence of vascular aging and increases the risk for cardiovascular disease (CVD). The age-associated increase in arterial stiffness is augmented in women after menopause, presumably due to estrogen deficiency. Telomeres, specialized DNA complexes at the ends of chromosomes, protect DNA and preserve the genome during replication. Longer leukocyte telomere length (LTL) is associated with longevity and resistance to CVD. Estrogen may regulate telomerase, the reverse transcriptase that adds telomeres to the ends of chromosomes, preserving LTL. We determined whether increased arterial stiffening across the stages of menopause is related to LTL shortening.

Methods: Participants were 124 healthy women (19-70y) classified as premenopausal (pre; n=36, 34±8y; mean±SD), early perimenopausal (early peri; n=24, 49±3y), late perimenopausal (late peri; n=25, 50±4y), or postmenopausal (post; n=39, 59 ± 5y). LTL was measured from genomic DNA isolated from peripheral blood mononuclear cells using quantitative real-time polymerase chain reaction. Arterial stiffness was measured using carotid artery compliance (inverse of stiffness) with ultrasound.

Results: Arterial compliance was progressively reduced across the stages of menopause (post 1.24±0.30; early peri 0.95±0.32; late peri 0.96±0.27; post 0.82±0.32 mmHg/milliliter, p<0.001). LTL tended to be shorter across menopause stages (pre 88±25; early peri 88±23; late peri 75±21; post 79±18 kilobases/diploid genome, p=0.06). LTL was positively correlated with arterial compliance (r=0.21, p=0.02), and inversely correlated with menopause stage (r= -0.19, p=0.04) and age (r= -0.19, p=0.04). The correlation between LTL and arterial compliance did not persist after controlling for menopause stage (r=0.14, p=0.13) or age (r=0.12, p=0.19).

Conclusion: These results suggest a potential mechanistic link between arterial stiffening and LTL across the stages of menopause. Future studies should investigate how estrogen regulates telomere length, including its effects on telomerase function, and how telomere shortening may mediate vascular aging. Longitudinal studies are needed to determine the effects of the changing hormonal environment with menopause, independent from those of age, on telomeres.

5.6 EFFECT OF AGE ON CEREBRAL BLOOD FLOW DYNAMICS FOLLOWING ACUTE RESISTANCE EXERCISE

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Aging decreases cerebral blood flow and increases cerebral pulsatility, an alteration that is associated with a greater prevalence of brain lesions and cognitive impairment. Resistance exercise (RE) is recommended for older adults for improving cardiovascular and metabolic risk factors. High-intensity RE is a potent stimulus that acutely increases blood pressure (BP) and reduces cerebral blood flow velocity (CBFv), resulting in greater flow pulsatility in cerebral circulation, which may damage cerebral microvasculature. Understanding the relationship between aging and cerebrovascular function in response to a physiological stress, like RE, in older adults is essential to help understand how to reduce the risk of cerebrovascular events. PURPOSE: To examine the effect of age on cerebral blood flow dynamics following acute RE in older adults compared with young adults. METHODS: Young (n=32, 26yrs, BMI: 24.0 kg/m2) and older (n=13, 58yrs, BMI: 29.3 kg/m2) adults performed maximal leg-extension/flexion RE (3x10 reps), with measurements at pre- and post-RE (Immediate, 5, 30-min). Heart rate (HR), BP (SBP, DBP, MAP), cardiac output (Q), CBFv of the middle cerebral artery, and end-tidal CO2 were collected. RESULTS: Mean and diastolic CBFv increased immediately post-RE in the young group (interaction, p<0.01) and decreased below baseline at 5-min post-RE (p<0.01) in both groups. CBFv pulsatility increased post-RE (p<0.01) in both groups, but continued to rise at 5-min post-RE in the young group (interaction, p<0.01). MAP was higher in the older group and increased immediate post-RE (p<0.01) in both groups. CONCLUSION: RE increased arterial BP in both groups; however, differential responses in the cerebral and systemic hemodynamics occurred between the young and older adults. Despite obtaining higher BP during RE in the older group, mean and diastolic CBFv did not increase post-RE. This differential age response indicates reduced cerebral hemodynamic responsiveness to RE with aging.

Table 1. Mean ± SD, *Exercise, †Group, ‡Interaction, p<0.05.
5.7 EFFECT OF L-CITRULLINE ON EXERCISE BLOOD FLOW IN OLDER WOMEN AND MEN

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Chronic L-citrulline (CIT) supplementation increases plasma L-arginine, and possibly nitric oxide bioavailability. Past studies have demonstrated improved NIRS-derived muscle oxygenation patterns during leg exercise following CIT supplementation in young men, but it is unknown if a similar finding would be observed in older adults. The purpose of this study was to test the hypothesis that exercise blood flow (BF) would be improved with CIT in older adults. Healthy older women (n=13, 70.2 ± 1.6y; mean ± SEM) and men (n=12, 71.1 ± 1.5y) completed a placebo controlled, double-blind, crossover trial. Participants were randomized to oral CIT (6 g/day) or placebo for 14 days, and switched to the other treatment for another 14 days after washout. The BF response to calf muscle exercise was measured in the right superficial femoral artery using Doppler ultrasound. Comparison was made between treatments on the change in BF from pre to post supplementation with adjustment for sequence and period effects.

The change in exercise BF was not different between treatments in women (CIT: 61.0 ± 21.3 vs. placebo: -19.7 ± 23.6 mL/min, p=0.51), but differed between treatments in men (CIT: 60.6 ± 21.4 vs. placebo: -19.7 ± 23.6 mL/min, p=0.01) such that the BF response to exercise was increased following CIT (pre: 447.8 ± 37.9 vs. post: 508.8 ± 47.8 mL/min, p=0.01) with no significant change following placebo (pre: 480.6 ± 37.9 vs. post: 460.9 ± 44.2 mL/min, p=0.42). These findings show a positive effect of L-citrulline on exercise-induced blood flow in older men, but not in women.

Study was funded by a Beginning Grant-in-Aid from the AHA Southwest Affiliate (15BGIA22710012)

5.8 INFLUENCE OF GENDER ON HYDRATION, LEAN MASS, STRENGTH, AND BLOOD PRESSURE IN OLDER ADULTS

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Overnight when intake is low, muscle can be depleted by fluid shifts to maintain blood pressure. This loss of intramuscular water may influence muscle force. We explored overnight changes in hydration, body composition, strength and blood pressure in 23 older adults (75.8 ± 1.3 years).

Methods: Men (n=9) and women (n=14) completed two testing sessions: mid-day euhydrated (Day 1) and early next morning dehydrated (Day 2). Hydration and body composition were measured with multi-frequency bioelectrical impedance. Strength was measured with hand grip dynamometry, arm curls, and chair stands. Blood pressure was measured using a sphygmomanometer.

Results: On Day 1, men had greater body weight (80.6±5.0 vs 68.5±3.3 kg, p<0.05), lean mass (59.8±3.0 vs 40.0±1.5 kg, p<0.001) and upper body strength (handgrip: 41.6±3.5 vs 22.2±1.6 kg, p<0.001; arm curls: 18.1±3.3 vs 14.9±0.8 curls, p<0.05) compared to women. This was accompanied by greater (p<0.001) total body water (47.0±1.5 vs 33.2±0.9 L), extracellular water (19.8±0.7 vs 15.8±0.4 L), and intracellular water (25.2±1.2 vs 17.5±0.6 L). However, there were no gender differences in positional changes in systolic (lying-sitting: -6.4±5.6 mmHg; sitting-standing: -7.6±2.1 mmHg) or diastolic (lying-sitting: -4.4±2.8 mmHg; sitting-standing: -7.3±2.3 mmHg) blood pressure. On Day 2, men and women experienced similar overnight losses in body weight (-0.9±0.1 kg, p<0.001), lean mass (-0.6±0.2 kg, p<0.01), and upper and lower body strength (hand grip: -1.6±0.4 kg, p<0.01; arm curls: -1.2±0.5 curls, p<0.05; chair stands: -1.1±0.5 stands, p<0.05), with a trend for loss of total body water (-0.4±0.2 L, p=0.08). Positional blood pressure was stable overnight except the change in systolic blood pressure between lying and sitting, which was significantly different on Day 1 than on Day 2 (+6.4±5.6 vs -4.4±2.8 mmHg, p<0.05), with a trend on Day 2 for less stability in men than women (-9.6±2.4 vs -11.4±4.2 mmHg, p=0.06).

Conclusion: In these older adults, both men and women had significant overnight loss of body water, lean mass, and strength, while positional blood pressure remained relatively stable. Based on these preliminary findings, greater lean mass does not influence the extent of overnight fluid loss or related loss of lean mass and strength, as loss did not differ by body size or muscle volume. The difference in positional systolic blood pressure observed on Day 2 is clinically non-significant and may be an anomaly.

5.9 DECREASED AGE-RELATED AUTONOMIC FUNCTION POSES A RISK FOR UNSTABLE CARDIOVASCULAR DYNAMICS: MONITORING CHANGES IN CIRCULATING BLOOD VOLUME

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In these older adults, both men and women had significant overnight loss of body water, lean mass, and strength, while positional blood pressure remained relatively stable. Based on these preliminary findings, greater lean mass does not influence the extent of overnight fluid loss or related loss of lean mass and strength, as loss did not differ by body size or muscle volume. The difference in positional systolic blood pressure observed on Day 2 is clinically non-significant and may be an anomaly.
**Introduction:** Autonomic function is important in the initial compensatory mechanism during blood volume changes and is important in monitoring a patient’s condition. However, few studies have investigated the effect of the aging on autonomic function and cardiovascular dynamics throughout changes in circulating blood volume.**Objective:** We examined the influence of aging on changes in autonomic function and cardiovascular dynamics, according to changes in circulating blood volume.**Methods:** We recorded the blood pressure (BP) and electrocardiographic data of 70 patients (mean age: 57.0 ± 14.2 years; 70.0% males) who were maintained in the supine position throughout autologous blood donation (200-400 mL; less than 10% of the circulating blood volume), as a model blood volume decrease. We subsequently administered fluid therapy with lactated Ringer's solution, using a volume equivalent to the volume of blood donated, as a model of blood volume increase. We analyzed heart rate variability parameters, including high frequency (HF) power spectra and the ratio of low frequency (LF) to HF power (LF/HF), to estimate parasympathetic and sympathetic nerve activity. Patients were divided into two groups based on a cut-off of 65 years, according to the World Health Organization’s definition of elderly people. The Tohoku University Graduate School of Medicine’s Ethics Committee approved this study (2014-1-378), which was conducted in conformance with guidelines for experimental procedures as set forth in the Declaration of Helsinki.**Results:** The LF component and HF component at rest decreased with age. In the ≥65-years group (n = 25), the LF component, HF component and LF/HF at rest were lower than in the <65-years group (n = 45). During blood volume changes, the HF component and LF/HF in the ≥65-years group remained lower than those in the <65-years group. The rate of change in heart rate (HR) and BP in the ≥65-years group fluctuated more than in the <65-years group, throughout blood volume changes.**Conclusion:** These results show that aging decreases autonomic function at rest and influences it continuously during a blood volume change of approximately 10% of the circulatory blood volume. This may cause increased fluctuation in HR and BP. These findings suggest that there is an underlying risk of circulatory failure in elderly people during the early stages of blood volume changes.

5.10**DEFECTIVE VASCULAR AUTOPHAGY IMPAIRS EXERCISE-INDUCED ACTIVATION OF ENDOTHELIAL NITRIC OXIDE SYNTHASE IN MICE**

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Molecular mechanisms regulating age-related changes in vascular function are only partly understood. Impairment of autophagy, the ubiquitous lysosomal trafficking pathway that regulates nutrient and redox homeostasis, is a common feature of aging at the cellular level. Earlier we showed that genetic or pharmacologic inhibition of autophagy in cultured bovine aortic endothelial cells (ECs) reduces shear stress-induced endothelial nitric oxide (NO) synthase (eNOS) activation and NO production. It is unknown whether aging impairs agonist-induced activation of autophagy and eNOS in the vasculature. Arteries from 2, 6, 17, and 24 month old C57Bl6 mice displayed a reduction in LC3 II : GAPDH protein expression and an increase in p62 : GAPDH accumulation, suggesting an age-associated decline in autophagy. While 14 h fasting increased LC3 II : GAPDH in arteries of 6-month old mice vs. random-fed controls, the upregulation was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS:GAPDH in arteries of 6-month old mice but was not observed in 24-month old animals.
data suggest that aging impairs agonist-induced activation of autophagy and eNOS in the vasculature. Next we explored how limited autophagic flux in ECs might precipitate reduced eNOS activation. In preliminary studies we observe that inhibiting autophagy in ECs impairs glycolytic ATP production to an extent that limits purinergic receptor signaling to PKCδ, an established positive regulator of eNOS. As a first step to determine translational relevance of this mechanism, 2-month old C57Bl6 mice were treated ± 3-methyladenine (3MA; 30 mg/kg IP), a class III PI3K inhibitor that blocks autophagosome formation. Thirty-min later mice completed 60-min treadmill running or were sedentary. Relative to the respective sedentary condition, acute exercise increased beclin-1 and Atg3 accumulation, p62 degradation, and increased GLUT1, p-PKCδ, and p-eNOS in arteries from vehicle-treated but not 3-MA treated mice. These data provide strong proof of concept that impaired vascular autophagy might compromise purinergic mediated eNOS activation. Supported by AHA 16GRNT31050004, NIH AG052848, University of Utah College of Health, Center on Aging, and Diabetes and Metabolism Center.

5.12 PREHYPERTENSION ACCELERATES VASCULAR AGING ACROSS THE MENOPAUSAL TRANSITION IN HEALTHY WOMEN

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Background: Endothelial dysfunction, characterized by impaired endothelial-dependent vasodilation, is a key feature of vascular aging and increases the risk for cardiovascular disease. We have previously shown that endothelial function is reduced across the stages of menopause in healthy women, presumably due to loss of estrogen. Pre-hypertension (120-139/80-89mmHg) similarly exacerbates vascular aging. In women, pre-hypertension may create an age/disease interaction that, combined with the loss of ovarian hormones, may further accelerate vascular aging. Therefore, we compared endothelial function in healthy normotensive and pre-hypertensive women across the stages of the menopause transition. Within the perturbations of a pre-hypertensive vasculature, we expected to see a more negative impact in pre-hypertensive women than in normotensive women as estrogen declines.

Methods: Endothelial function (brachial artery flow-mediated dilation; FMD) was measured in 192 healthy women (19-70y) classified as premenopausal (n=51, 34±8y; mean±SD), early perimenopausal (n=24, 49±3y), late perimenopausal (n=26, 50±4y), early (≤5y) postmenopausal (n=40, 55±3y), or late (>5y) postmenopausal (n=51; 60±4y). Women were further classified as normotensive (<120/80mmHg, n=120) or pre-hypertensive (120-139/80-89mmHg, n=72).

Results: Brachial artery FMD was progressively reduced across stages of menopause (P<0.001). At each stage, FMD was lower in pre-hypertensive vs normotensive women (P<0.001: premenopausal (10.7±3.3 vs 9.3±1.8); early perimenopausal (8.7±2.9 vs 7.5±2.1); late perimenopausal (7.5±2.1 vs 5.8±1.6); early postmenopausal (6.0±1.8 vs 5.1±1.8); late postmenopausal (5.4±1.5 vs 4.5±2.0). Adjusting for age did not influence the main effects of menopausal stage (P=0.003) or blood pressure category (P=0.004).

Conclusion: These data demonstrate that prehypertensive women experience proportionally greater declines in endothelial function across the stages of menopause than their normotensive peers. This suggests that prehypertension may contribute to an age-disease interaction in healthy women. Future investigations should evaluate lifestyle interventions and whether maintaining or improving blood pressure, particularly during the menopause transition, slows the progression of vascular aging and prevents cardiovascular disease.

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5.13 OXIDATIVE STRESS CONTRIBUTES TO AGE-ASSOCIATED REDUCED LEFT VENTRICULAR DIASTOLIC FUNCTION IN MEN

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Introduction: Left ventricular (LV) diastolic function declines with age, even in healthy adults. A possible mechanism for the age-related decline in LV diastolic function may be a functional maladaptation to an imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant defenses (i.e., “oxidative stress”). Whether oxidative stress contributes to reduced LV diastolic function in aging men is unknown. Methods: LV diastolic function (transhachoracic echocardiography; peak early [E] to late [A] mitral inflow velocity ratio [E/A], and peak early [E] mitral inflow velocity to peak early [e’] mitral annular velocity ratio [E:e’]) was measured during intravenous infusion of saline (control) and during supraphysiological intravenous infusion of the potent antioxidant Vitamin C in healthy young (n=12, 30±5 yrs; mean±SD) and older men (n=7, aged 65±6 yrs). Results: Compared to young men, older men had a ~45% lower mitral valve E/A ratio (1.24±0.13 vs 2.26±0.23, p<0.01) and a ~40% higher sepal E:e’ and lateral E:e’ (10.4±0.9 vs 6.1±0.4, p<0.01, and
49±3 yr) and late (N=24, 50±3 yr) perimenopausal, and early were measured in 144 healthy women categorized as serum MMP2, MMP9, TIMP1 and TIMP2 concentrations (P=0.025) and TIMP2 (r= -0.21, P=0.018). Circulating activity. FMD was inversely correlated with MMP2 (r=-0.19, P<0.05), indicating reduced proteolytic activity, proteolytic potential, and ECM degradative capacity) compared to late perimenopausal women (all P<0.05). There was no significant effect of Vitamin C on the mitral valve E/A ratio (1.1±0.2,NS) in older men, however E/A ratio decreased during Vitamin C infusion in young men (to 1.95±0.16, p<0.01), indicating a decrease in LV diastolic function possibly related to a disruption and shift in redox balance to a pro-oxidant state. Conclusion: These preliminary findings support oxidative stress as a potential mechanism for the age-related decline in LV diastolic function in men. Future studies should determine the mechanisms by which ROS alters LV diastolic function and whether chronic exposure to endogenous antioxidants attenuates or reverses the decline in LV diastolic function with aging. Support: NIH R01AG049762, P30 DK048520, U1L TR001082; Eastern Colorado VA Geriatric Research, Education, and Clinical Center.

5.14 
EXTRACELLULAR MATRIX REMODELING PROTEASES AS A FUNCTION OF MENOPAUSE STAGE: IMPACT ON VASCULAR AGING
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Background: Vascular aging, featuring large artery stiffening and endothelial dysfunction, is accelerated in women during the menopause transition. Matrix metalloproteinasises (MMPs) and tissue inhibitors of MMPs (TIMPs) impact vascular aging by regulating extracellular matrix (ECM) turnover and remodeling. We determined whether MMPs and TIMPs are mechanistically related to vascular aging across menopause stages. Arterial stiffness (carotid artery compliance with ultrasound), endothelial function (brachial artery flow-mediated dilation, FMD), and serum MMP2, MMP9, TIMP1 and TIMP2 concentrations were measured in 144 healthy women categorized as premenopausal (N=38, 34±8 yr, mean±SD), early (N=24, 49±3yr) and late (N=24, 50±3 yr) perimenopausal, and early (N=27, 55±3 yr) and late (N=31, 61±5 yr) postmenopausal. Results: Arterial compliance and FMD were reduced across menopause stages. MMP9 was different across menopause stages (P<0.003), with higher concentrations in late perimenopausal compared to premenopausal women, and lower concentrations in both early and late postmenopausal compared to late perimenopausal women (all P<0.05). There were no significant differences in MMP2, TIMP1, or TIMP2 concentrations. MMP9/TIMP1 ratio (marker of net MMP activity, proteolytic potential, and ECM degradative capacity) was different across menopause stages (P<0.005), with a lower ratio in late postmenopausal women compared to late perimenopausal (P<0.05), indicating reduced proteolytic activity. FMD was inversely correlated with MMP2 (r=-0.19, P=0.025) and TIMP2 (r=-0.21, P=0.018). Circulating estrogen concentrations were positively correlated with MMP9 (N=97, r=0.39, P<0.01) and MMP9/TIMP1 ratio (N=91, r=0.38, P<0.01). Age was positively correlated with TIMP2 (r=0.19, P=0.025). Conclusion: These data suggest that the menopause transition is associated with alterations in ECM remodeling proteases, favoring greater ECM accumulation. These ECM proteases may play a role in endothelial dysfunction in vascular aging. Whether serum MMPs and TIMPs reflect concentrations at the local vascular level, and whether and how they are mechanistically linked to vascular aging across the menopause transition, warrants further study. Support: NIH R01s AG027678, AG22241, AG049762, R56HL114073, K01AG20683, P30 DK048520 and U1L TR001082, University of Colorado Denver (UCD) Center for Women’s Health Research, and Eastern Colorado VA Geriatric Research, Education, and Clinical Center.

5.15 
ACUTE NITRATE SUPPLEMENTATION ATTENUATES PROGRESSIVE ISCHEMIC EXERCISE-INDUCED PRESSOR RESPONSES IN POSTMENOPAUSAL WOMEN
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Older (postmenopausal) women have exaggerated blood pressure (BP) responses during static exercise, as well as during post-exercise circulatory arrest (PECA), suggesting an enhanced metaboreflex and altered autonomic control of BP. These BP responses are prognostic for future hypertension, adverse cardiovascular events, and mortality. Intriguingly, dietary nitrate supplementation has shown beneficial effects on contracting muscle perfusion (Casey et al., 2015) and metabolite accumulation (Bailey et al., 2010; Bailey et al., 2009). However, its effects on the regulating BP in postmenopausal women have not been investigated. PURPOSE: We tested the effects of acute nitrate supplementation on reflex increases in BP evoked by progressively restricting blood flow to the exercising forearm in healthy postmenopausal women. We hypothesized that dietary nitrate supplementation would attenuate the increases in BP during graded muscle ischemia and metaboreflex isolation. METHODS: In a randomized, double-blind, crossover study, eight healthy postmenopausal women (60 ± 1 years) consumed a concentrated beetroot juice supplement (BPplacebo; 140 mL Beet-It Organic, James White Juice Company) or nitrate-depleted beetroot juice as a placebo (BPplacebo; 140 mL nitrate-depleted Beet-It Organic, James White Juice Company) on separate visits at least 7-days apart. On each visit, subjects performed low intensity intermittent handgrip exercise (10% of MVC, 30 contractions/min) until volitional fatigue followed by 3-min
of PECA. During the exercise, muscle blood flow was restricted progressively as follows: After 4-min of free flow exercise period, a BP cuff on the subject’s upper arm was progressively inflated starting from 20 mmHg at a rate of 20 mmHg/min. BPs and HR were recorded continuously throughout the experiment. **RESULTS:** Acute dose of BR_brand raised plasma NO3 and NO2 compared to BR_placebo (all p<0.05). BPs steadily increased with exercise during both visits (p<0.05), and time course of peak BP responses tended (all p<0.05). BPs steadily increased with exercise during both periods, with BR_nitrate (vs. BR_placebo; P=0.17). Moreover, nitrate supplementation alters reflex increases in BP at volitional fatigue (25±5% vs. BR_placebo, 30±5%; p<0.05). During PECA period, no intervention effect was observed on the reductions in HR and SBP. DBP during PECA decreased to a greater extent with BR nitrate, but there wasn’t a significant difference (vs. BR_placebo; P=0.18). **CONCLUSION:** These results suggest that acute nitrate supplementation alters reflex increases in BP at fatigue during progressive ischemic forearm exercise, and warrant continued investigation of nitrate supplementation and reflex control of the circulation during exercise in postmenopausal women.

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5.16 THE IMPACT OF MENOPAUSAL STAGE AND AEROBIC FITNESS ON ENDOThelial FUNCTION AND RESPONSES TO ACUTE EXERCISE

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Cardiovascular disease risk increases with menopause; however, whether this change effects endothelial function and if fitness modulates any effects on endothelial function remains largely unexplored. **PURPOSE:** To determine if there are differences in endothelial function before and after acute exercise in healthy peri- and post-menopausal women with disparate levels of aerobic fitness. **METHODS:** High and low fit (HIGH, n=15; LOW, n=15) peri- and postmenopausal women (PERI, n=16; POST, n=14) completed 30min of treadmill exercise at 60-64% VO2peak. Brachial artery flow-mediated dilation (FMD) was measured twice before and after exercise. Artery diameter and blood flow were continuously measured during 2min of baseline, 5min of forearm blood flow occlusion (200mmHg), and 4min post-occlusion. FMD was calculated as (Diameterpeak - Diameterbaseline)/ Diameterbaseline x 100. Shear rate area-under-the-curve (SR AUC) to peak dilation and time to peak dilation (TTP) were calculated. Data was analyzed for differences by group (PERI vs. POST), condition (HIGH vs. LOW), and time (pre-vs. post-exercise) using ANOVAs and is expressed as mean±SEM. FMD data on LOW PERI and POST was previously published. **RESULTS:** Overall, FMD was higher in PERI compared with POST (PERI: 6.9±1.0% vs. POST: 5.0±1.0%, p=0.03), independent of fitness. There was a main effect of fitness on FMD (p=0.024), with no difference in pre-exercise FMD (HIGH: 5.0±1.7% vs. LOW: 6.5±1.3%, p=0.205) but lower FMD in HIGH after acute exercise (HIGH: 5.0±1.1% vs. LOW: 7.3±1.4%, p=0.05). Before exercise, FMD did not differ by fitness in PERI (p=0.271), but was lower in HIGH compared to LOW POST (HIGH: 3.3±1.5% vs. LOW: 6.5±0.5%, p=0.038). Repeated FMD trials lead to a lower FMD response in LOW POST (pre-exercise 1: 7.7±1.1%, pre-exercise 2: 5.3±1.0%, post-exercise 1: 7.8±1.5%, post-exercise 2: 4.5±1.0%, p=0.03) but not HIGH POST (pre-exercise 1: 2.1±1.0%, pre-exercise 2: 4.6±2.2%, post-exercise 1: 4.3±1.6%, post-exercise 2: 4.0±1.0%, p=0.46). Reported differences in FMD were independent of SR AUC and baseline diameter. There was a main effect of menopausal status on TTP (p=0.03), with higher TTP in POST before (PERI: 45.4±5.5s vs. POST: 65.9±10.4s, p=0.05) but not after acute exercise (PERI: 54.2±4.0s vs. POST: 65.3±13s, p=0.273). **CONCLUSION:** Endothelial function appears to worsen with menopause, independent of fitness; however, fitness may improve endothelial responsiveness to repeated FMD trials and appears to modulate the response to acute exercise. FMD in HIGH POST was low despite few CVD risk factors in this group. Further investigation is warranted to understand the impact of fitness on endothelial function in aging women.

Funding Sources: American College of Sports Medicine Foundation Doctoral Student Grant (Serviente) & University of Massachusetts Amherst Faculty Research Grant (Witkowski).

5.17 VAGAL MODULATION OF HEART RATE BY THE ARTERIAL BAROREFLEX IN MIDDLE-AGED WOMEN: A POTENTIAL INFLUENCE OF REPRODUCtIVE AGE

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Measures of cardiac autonomic function are reduced with advanced chronological age in both sexes (LaBittin et al., 1998; Tank et al, 2000), and this reduction may partly explain the increased cardiovascular morbidity and mortality observed in older adults. In women, however, the potential for reproductive aging to contribute to the age-related decline in vagal modulation of cardiac activity has remained largely under-examined. Thus, the **PURPOSE** of the present study was to investigate whether cardiovagal baroreflex sensitivity (BRS) is influenced by menopause transition stage in a sample of healthy middle-aged women. **METHODS:** Women (41 – 59 yrs.) were categorized into early perimenopausal (n =12), late perimenopausal (n = 8), and early postmenopausal (n = 9) stage groups based on self-reported bleeding history using the Stages of Reproductive Aging Workshop criteria. Beat-to-beat arterial blood pressure (Finometer midi) and heart rate (ECG) were continually collected during 10 minutes of spontaneous breathing while resting in the supine position. Cardiovagal BRS was subsequently determined by averaging the
increasing and decreasing systolic blood pressure and R-R regression coefficients of corresponding sequences of early postmenopausal women (p = 0.017). In the combined sample of women, cardiovasal BRS was best explained by a model containing systolic blood pressure and a marker of reproductive aging (follicle-stimulating hormone; $r^2 = 0.57$, p < 0.001).

CONCLUSIONS: Collectively, these findings provide evidence that reproductive aging may contribute, at least in part, to the age-associated decline in cardiovasal BRS in women.

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5.18 MORE ACCURATE SYSTOLIC BLOOD PRESSURE MEASUREMENT FOR IMPROVED HYPERTENSION MANAGEMENT IN ELDERLY
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Since excessive lowering of blood pressure can lead to adverse side-effects, its accurate measurement is essential for safe control. However, currently available automatic blood pressure measurement devices, based on oscillometry, are prone to significant errors (errors of 10-15 mmHg are common), mainly due to indirect determination of the blood pressure from the oscillometric air-pressure waves. Errorneous measurement by 10-15 mmHg can lead to a similar unintended reduction of systolic blood pressure and may adversely affect patients treated to a systolic blood pressure of 120-130 mmHg. In particular, in the elderly, inaccurate systolic blood pressure measurement can lead to excessive blood pressure lowering, increase the risk of hypotension and consequently lead to hypo-perfusion to vital organs, including the brain. A novel technique for systolic blood pressure measurement, based on photoplethysmography, was found to be more accurate than the available automatic oscillometric technique, enabling more precise automatic systolic blood pressure measurements, in the home and clinic. More accurate systolic blood pressure measurement allows both optimal and safer control of blood pressure.

6.0 SYMPOSIUM: NOVEL MECHANISMS OF BLOOD FLOW CONTROL AND MICROVASCULAR FUNCTION WITH AGE

6.1 SKELETAL MUSCLE OXYGEN TRANSPORT DURING EXERCISE: EFFECTS OF AGING AND HEART FAILURE.
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Chronic heart failure (CHF) represents a “perfect storm” of multiple organ dysfunction that impacts critically the O$_2$ transport system (↑ O$_2$ requirements, ↓ O$_2$ availability), culminating in impaired muscle function and exercise intolerance. CHF afflicts over 5 million Americans the vast majority of whom are aged 65+ years. However, within established CHF animal models there is a dearth of investigations examining aged individuals - the condition of most direct relevance to human health. Whereas CHF in the aged may be a pathophysiologically different disease than in younger counterparts both manifestations are characterized by reduced nitric oxide (NO) bioavailability. Within skeletal muscle, CHF and aging impair arteriolar vasoilation and perturb capillary hemodynamics disrupting the O$_2$ delivery-to-utilization/requirement balance. The predations of both CHF and aging coalesce at O$_2$’s final frontier – the blood-myocyte interface – to reduce microvascular O$_2$ pressure and O$_2$ diffusing capacity. This O$_2$ transport deficit is resistant to current traditional therapies. However, increasing NO bioavailability via dietary nitrate supplementation elevates skeletal muscle blood flow and vascular conductance whilst simultaneously reducing the O$_2$ cost of exercise. This therapeutic strategy is targeted towards muscles and muscle regions with low microvascular O$_2$ pressures and reduced pH (both of which impair endogenous NO synthase function). We present evidence that nitrate supplementation can restore capillary hemodynamics in CHF and improve contracting muscle microvascular O$_2$ pressures and O$_2$ diffusing capacity. This strategy has great potential to improve the efficacy of cardiac rehabilitation and patient quality of life and reduce morbidity and mortality in CHF. Support: HL-108328 and AHA 4350011. REFERENCES: Ferguson, S.K., C. T. Holdsworth, T.D. Colburn, J.L. Wright, J.C. Craig, A.J. Fees, A.M. Jones, J.D. Allen, T.I. Musch, and D.C. Poole. Dietary nitrate supplementation: Impact on skeletal muscle vascular control in exercising rats with chronic heart failure. J Appl Physiol. 121:661-9, 2016.

6.2 REGULATION OF SKELETAL MUSCLE BLOOD FLOW DURING EXERCISE IN AGING HUMANS
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The regulation of blood flow and oxygen delivery to contracting skeletal muscle is complex and involves the mechanical effects of muscle contraction; local metabolic, red blood cell and endothelium-derived substances; and the sympathetic nervous system (SNS). With advancing age in humans, skeletal muscle blood flow is typically reduced
during dynamic exercise and this is due to a lower vascular conductance, which could ultimately contribute to age-associated reductions in aerobic exercise capacity, a primary predictor of mortality in both healthy and diseased aging populations. Recent findings from our laboratory and others have highlighted the role of impaired endothelial control of blood flow to contracting muscle of older adults. In this context, impaired nitric oxide availability due to scavenging by reactive oxygen species, in conjunction with elevated vasoconstrictor signaling via endothelin-1, reduces the local vasodilatory response to muscle contraction in older adults. Additionally, aging impairs the ability of contracting skeletal muscle to blunt sympathetic vasoconstriction (i.e. “functional sympatholysis”), which is critical for the proper regulation of tissue blood flow distribution and oxygen delivery, and could further reduce skeletal muscle perfusion during high intensity and/or large muscle mass exercise in older adults. More recently, observations from our laboratory strongly suggest that initiation of endothelium-dependent hyperpolarization (EDH) is the underlying signaling event necessary to properly modulate sympathetic vasoconstriction in contracting muscle, and that age-associated impairments in red blood cell adenosine triphosphate release and stimulation of EDH may explain impairments in both local vasodilation and functional sympatholysis with advancing age in humans.

6.3 THE IMPACT OF AGE AND HYPERTENSION ON CUTANEOUS MICROVASCULAR FUNCTION

Lacy Alexander

Microvascular dysfunction, characterized by attenuated endothelium-dependent vasodilation, augmented vasoconstriction, and eutrophic remodeling occurs via distinct mechanisms in primary human aging vs. hypertensive pathology. The human cutaneous circulation is an accessible model for examining mechanisms underlying microvascular dysfunction in humans. Impaired vasoactivity in the cutaneous microcirculation is detectable prior to impairments in conduit artery function, and occurs to a similar magnitude and via the same mechanisms as microvascular damage to the coronary, renal, and skeletal muscle circulations. Thermal and pharmacological stimuli, combined with traditional biochemical approaches, provide a powerful in vivo bioassay allowing for the targeted pharmaco-dissection of distinct mechanisms underlying cutaneous microvascular dysfunction as well as a tool for examining the potential impact of lifestyle and pharmacological intervention strategies. Emerging data in the human cutaneous circulation indicate that enzymatically produced hydrogen sulfide (H\textsubscript{2}S) is an important endothelium-derived hyperpolarizing factor. There are multiple enzymatic sources of H\textsubscript{2}S in the cutaneous microvasculature including cystathione γ-lyase, and 3-mercaptopyruvate trans-sulfurase. H\textsubscript{2}S is capable of modulating vascular function through extensive cross talk with the NO signaling pathway at multiple regulatory points. Further, the H\textsubscript{2}S and NO pathways appear to be differentially regulated in primary aging vs. hypertension. Emerging data suggest that points along the H\textsubscript{2}S enzymatic pathway may be specific molecular targets for the development of treatment strategies for age and hypertensive vascular pathology. Additionally, new putative targets for pathology-associated vascular remodeling will be discussed. NIH HL093238 REFERENCES Debbabi, H., et al., *Noninvasive assessment of endothelial function in the skin microcirculation*. Am J Hypertens, 2010. 23 (5): p. 541-6. Khan, F., et al., *Relationship between peripheral and coronary function using laser Doppler imaging and transthoracic echocardiography*. Clin Sci (Lond), 2008. 115 (9): p. 295-300. Coulon, P., J. Constans, and P. Gosse, *Impairment of skin blood flow during post-occlusive reactive hyperemia assessed by laser Doppler flowmetry correlates with renal resistive index*. J Hum Hypertens, 2011. Jung, F., et al., *Microcirculation in hypertensive patients*. Biorheology, 2013. 50 (5-6): p. 241-55.

6.4 MICROVASCULAR ADAPTATIONS DURING AGING: OPPORTUNITIES FOR NEW MODELS AND DISCOVERIES

Walter Murfée

Microvascular network growth and remodeling are common denominators for most age-related pathologies. In multiple pathologies (cancer, retinopathies, rheumatoid arthritis) blocking microvascular growth, termed angiogenesis, would be beneficial. In others (myocardial infarction, stroke, hypertension), promoting angiogenesis would be desirable. Most therapies, however, are developed using adult animal models. This approach is problematic and does not account for the impaired angiogenesis and the inherent network structure changes that might result from age. Considering the common conception that angiogenesis is impaired with age, a need exists 1) to study the causes and mechanisms of angiogenesis in aged scenarios and 2) to develop new tools to enable comparison of aged versus adult responses to therapy. The objective of this presentation will be to introduce novel cell changes along aged microvascular networks and a new angiogenesis ex vivo tissue culture model for aging research. Immunolabeling of mesenteric microvascular networks harvested from Aged (24 mo.) versus Adult (9 mo.) male Fischer 344 rats identified an increased vascular pericyte coverage along capillaries in aged networks. This finding suggests a novel hypothesis that pericytes might play a role in aging impaired angiogenesis and motivates the need to probe spatio-temporal pericyte-endothelial cell interactions. Culturing the rat mesenteric tissues potentially provides such a model as both cell types remain viable and functional across the hierarchy of intact networks. Our results will highlight the opportunity for advancing our scientific tools and understanding of how and why microvascular network growth is altered in aged tissues. This work is supported by NIH AG049821. REFERENCE: Sweat, RS, Sloas DC, Stewart SA, Czarny-Ratajczak M, Baddoo M, Eastwood JR, Suarez-Martinez AD, Azimi MS, Burks HE, Chedister LO, Myers L, and Murfée WL. (2017). Aging is associated with impaired angiogenesis, but normal microvascular network structure, in the rat mesentery. *Am J Physiol Heart Circ Physiol*. 312(2):H275-H284.
8.0 SYMPOSIUM: NOVEL IMPLICATIONS FOR BLOOD FLOW AND VASCULAR DYSFUNCTION IN NON-CARDIOVASCULAR RELATED DISEASES

8.1 IMPLICATIONS FOR BLOOD FLOW IN PROSTATE CANCER: TUMOR/SYSTEMIC INTERACTIONS, CENTRAL AND PERIPHERAL CARDIOVASCULAR FUNCTION

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Cancer is considered an accelerated model of aging, largely due to a reduced aerobic capacity at any point after treatment (e.g., 10+ years) compared to healthy age-matched counterparts. The reduced aerobic capacity is attributed to the deleterious effects of cancer treatment(s). Exercise training has been shown to benefit cancer patients, largely by mitigating the side effects of treatment and increasing therapy tolerance. We are interested in investigating 1) how exercise can impact tumor/systemic interactions and the subsequent effect on tumor oxygenation as the first step in understanding how exercise training may impact cancer treatment, and 2) whether cancer itself, independent of treatment, can impact indices of aerobic capacity and the regulation of skeletal muscle blood flow at rest and during exercise. In pre-clinical models of prostate cancer, during exercise there is a large increase in tumor blood flow that is associated with a down-regulation of several vasoconstrictor pathways of the tumor resistance vasculature. When comparing skeletal muscle (soleus) blood flow at rest and during exercise, cancer did not affect resting muscle blood flow, but significantly reduced the change in muscle blood flow to moderate-intensity exercise (reduced rest-exercise muscle perfusion), indicating potential vascular dysfunction within the periphery. When looking at fatigue and central indices of cardiovascular function, time-to-exhaustion in a treadmill exercise test was reduced with cancer, and tumor mass was significantly correlated with reduced LV function (i.e., LV DP/DT). These data suggest that 1) exercise may be a useful intervention to modulate tumor hypoxia and blood flow and, 2) cancer, independent of treatment, hastens the onset of fatigue, likely due to reduced central and peripheral cardiovascular function. Given the multifaceted negative impact of aging on the cardiovascular system, it is likely that cancer induced cardiovascular dysfunction is potentiated in aging subjects. (American Cancer Society (RSG-14-150-01-CCE to BJB) McCullough, D.J., J.N. Stabley, D.W. Siemann, B.J. Behnke. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. J. Natl. Cancer Inst. Apr; 106(4):dju036. Doi 10.1093/jnci/dju036.

8.2 ENDOThelial DYSFUNCTION IN THE ADIPOSE: A KEY REGULATOR OF AGe RELATED METABOLIC DYSFUNCTION?

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While once thought to be an inert site of energy storage, the adipose tissue is now appreciated as a dynamic endocrine organ that, when dysfunctional, contributes to both metabolic and cardiovascular disease risk. The adipose tissue contributes to metabolic homeostasis by buffering plasma free fatty acids, limiting ectopic lipid accumulation and secreting adipokines and cytokines that can influence metabolism, inflammation, and appetite. It is well appreciated that adipose dysfunction is a consequence of obesity. This dysfunction, characterized in part by adipose hypertrophy and inflammation, is known to contribute to the tissue and systemic metabolic dysfunction that occur in obesity. Less is known, however, about the consequences of aging on the function of the adipose and its interlaying vasculature or their role in age-associated metabolic dysfunction. Like obesity, advanced age also leads to adipose tissue dysfunction and inflammation that is comitant with metabolic impairments, but in contrast, this occurs despite a reduction in adipose mass. Although the mechanisms underlying reduced adipose tissue mass and the concomitant adipose dysfunction with advancing age are incompletely understood, dysfunction of the arteries within the adipose tissue may be a significant factor. With aging, both endothelial function and angiogenic capacity are impaired in the adipose tissue and this arterial dysfunction may contribute to tissue inflammation and hypoxia that characterizes adipose dysfunction. A better elucidation of the mechanisms underlying adipose artery dysfunction with advancing age may provide important insight into treatment strategies to reduce metabolic and vascular diseases in older adults.

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11.0 SYMPOSIUM: NOVEL MECHANISMS UNDERLYING VASCULAR IMPAIRMENTS IN THE AGING BRAIN

11.1 PULSE PRESSURE IN THE AGING BRAIN

Eric Thorin1
The major cause of peripheral arterial stiffening is aging, and this is accelerated by sedentariness, hypertension, diabetes and atherosclerosis; in these conditions, the biomechanics of the cerebral arteries are poorly understood. When combined, sedentariness, hypertension, obesity, elevated glucose and lipids are associated with a 2- to 4-fold rise in the risk of brain infarction. Furthermore, physical inactivity alone is a greater risk factor for stroke than for myocardial infarction and there is evidence that sedentariness increases dementia. A major benefit of regular exercise, which can acutely increase blood pressure to 200 mm Hg, is the maintenance of the cerebrovascular endothelial function and wall structure. Increase in aortic stiffness has been reported to be associated with increased carotid flow augmentation (blood acceleration during systole) and pulsatility of blood flow in the middle cerebral artery (MCA). In human, chronic increases in systemic pulse pressure are associated with cerebrovascular damage, leading to the so-called pulse-wave encephalopathy. Several studies have established a link between peripheral arterial stiffness responsible for the sustained increase in pulse pressure and brain microvascular diseases such as cerebral small vessel disease, cortical gray matter thinning, white matter atrophy and cognitive dysfunction in older individuals, hypertensive and diabetic patients. In addition, the higher pulsatility of CBF is positively correlated with the loss of white matter integrity. Finally, the rarefaction of white matter is strongly associated with MCA pulsatility that is strongly dependent on aortic pulse pressure and large artery stiffness. Thus, physiopathological conditions characterized by an increase in peripheral artery stiffness and thus pulse pressure, are associated with brain damage and structural changes.

11.2 AGING INCREASED BLOOD PRESSURE AND ALTERS THE BIOMECHANICAL PROPERTIES OF THE POSTERIOR CEREBRAL ARTERIES AND THE PARENCHYMAL ARTERIOLES

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Artery dysfunction is an important determinant of cardiovascular diseases such as hypertension, atherosclerosis and cerebral artery disease which are major causes of mortality in the elderly. Cerebral artery remodeling, described as a change in artery structure, could also play an important role in dementia development. To assess the effects of aging on the biomechanical properties and structure of the cerebral vasculature and we elected to study two artery types, the posterior cerebral arteries (PCAs) and parenchymal arterioles (PAs). The PCAs are relatively large pial arteries while the PAs are smaller arterioles that dive into the brain parenchyma, these smaller vessels regulate the perfusion of the microcirculation where nutrient and gas exchange occurs. The biomechanical properties of the PCAs and PAs from young (3-5 months old) and aged (22-24 months old) were assessed by pressure myography. Significantly different (p<0.05) data are presented as mean ± SEM; young vs old (n=9 in each group). In the PCA, older mice had increased outer (155.6 ± 3.2 vs 169.9 ± 3.2μm) and lumen (116.4 ± 3.6 vs 137.1 ± 4.7μm) diameters. Wall stress (375.6 ± 35.4 vs 504.7 ± 60.0 dynes/cm²) and artery stiffness (β-coefficient: 5.2 ± 0.3 vs 7.6 ± 0.9) were also increased. However, wall strain (0.8 ± 0.1 vs 0.6 ± 0.1) was reduced with age. In the PAs from old mice, wall thickness (3.9 ± 0.3 vs 5.1 ± 0.2μm), and area (591.1 ± 95.4 vs 852.8 ± 100μm²) were increased while stress (758.1 ± 100.0 vs 587.2 ± 35.1 dynes/cm²) was reduced. Blood pressure was measured by telemetry in a small group of young (n=3) and aged (n=4) mice. Aging increased mean arterial (104.6±0.25 vs 118.5±0.24mmHg) and pulse pressures (0.36.57±1.84 vs 47.83±0.36mmHg). Preliminary studies suggest that the aged mice also exhibited artery rarefaction, and increased calcium and collagen deposition. We conclude that age-associated remodeling occurs in large cerebral arteries and arterioles and may increase the risk of cerebrovascular disease.

11.3 HUMAN CEREBRAL ARTERY FUNCTION AND AGING

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Aging is associated with vascular dysfunction, elevated cardiovascular disease risk, and increased Alzheimer’s disease (AD) pathology. In addition, aging reduces cerebral perfusion and cerebral arterial function, and is associated with brain atrophy. Understanding the effects of physiological aging on cerebral blood flow and brain structure may help to determine effective strategies to mitigate these effects on the population. Currently, cerebral blood flow regulation during midlife is poorly understood, making it difficult to distinguish age-related physiology from AD-related pathophysiology. Furthermore, age-related changes in the vasculature may accelerate pathophysiological increases in neurodegeneration and AD neuropathology. Understanding how cerebral arterial function changes, especially during midlife, is important because this is the critical period where lifestyle and pharmacological intervention can modify the risk of future cognitive impairment. Exercise may be one strategy to prevent or delay cognitive decline. Regular exercise has been shown to improve cognition, likely through beneficial adaptations in cerebral arterial function. Additional interventions initiated during midlife that are directed at improving cerebral perfusion and cerebral arterial function are necessary. Support: NIH AG038067 and HL118154.

11.4 ROLE OF ENDOTHELIAL NOS IN AGE-RELATED MICROVASCULAR IMPAIRMENTS

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Endothelial cells have been shown to express endothelial (eNOS) and neuronal (nNOS) isoforms of nitric oxide synthase. Although eNOS has been extensively studied in aging vasculature, we know very little about the expression, the pathophysiological role, or the regulation of nNOS in the brain microvessels in aged animals. For the first time, we have identified the expression of nNOS in the primary cultured brain microvascular endothelial cells from mice, rats, and humans; and the freshly isolated rat brain microvessels. Lack of nNOS expression in endothelial cells in the nNOS knockout mice further confirmed the presence of nNOS in the endothelial cells. Inhibition of nNOS by pharmacological and RNAi approaches showed that endothelial nNOS is constitutively active and does not produce NO but instead produces superoxide. Interestingly, inhibition of nNOS by the same pharmacological inhibitors in primary cultured cortical neurons showed that nNOS of neuronal origin produces NO but not superoxide. Thus, endothelial nNOS is distinct from nNOS of neuronal origin as well as eNOS. The impact of aging on the endothelial nNOS was examined in the freshly isolated brain microvessels from young (10 weeks) and middle aged Sprague Dawley (18 month) rats. Although the expression levels of nNOS was found to be not significantly different, endothelial nNOS in the aged microvessels does not produce superoxide. Furthermore, supplementation of tetrahydrobiopterin attenuated the endothelial nNOS activity suggesting that it exists physiologically in an uncoupled state possibly localized in a subcellular compartment lacking access to tetrahydrobiopterin. Therefore, we examined the effects of pharmacological inhibition of nNOS on the mitochondrial respiration by measurements of oxygen consumption rate in the isolated heart mitochondria. We found that nNOS inhibitors enhanced the proton leak and reduced the ATP production in isolated heart mitochondria of young rats which were lost in the middle-aged rats. Thus, aging is associated with the alterations of endothelial and mitochondrial nNOS activity. This work is supported by: NIH grant (NS094834) and AHA Scientist Development Grant (14SDG20490359).

### 12.2 AGE-RELATED ARTERIAL ALU ELEMENT INSTABILITY AND SURVIVAL IN MELANOMA PATIENTS

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**Background:** Highly repetitive short interspersed ALU elements are hot-spots for genomic structural mutations. In cancer patients, age-related ALU element instability in arteries could contribute to arterial functional changes that promote cancer progression and increase mortality rates.

**Objective:** To determine if ALU element instability occurs with advancing age in arteries from patients with non-metastatic melanoma and influences risk for mortality from metastatic disease during a 5-year follow-up period in a subgroup of age-matched patients.

**Methods:** ALU element instability was assessed in 88 small feed arteries obtained from routine sentinel lymph node biopsies by measuring ALU element content per genome by qPCR. ALU element damage was assessed by the DNA break marker, serine 139 phosphorylated histone γ-H2A.X (γ-H2), at ALU elements by ChIP. Apoptotic signaling was assessed by p53 bound to the BAX gene promoter by ChIP.

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*12.0 SYMPOSIUM: CELLULAR SENESCENCE AND GENOMIC INSTABILITY: IMPLICATIONS FOR CARDIOVASCULAR DISEASE*

**12.1 CELLULAR SENESCENCE AND SENOLYTIC AGENTS IN AGE-RELATED DYSFUNCTION AND CHRONIC DISEASES**

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Senescent cells, which are resistant to apoptosis, can secrete a range of pro-inflammatory cytokines and chemokines, matrix-destroying proteases, factors that cause stem cell dysfunction, and hemostatic factors, the senescence-associated secretory phenotype (SASP). We developed senolytic agents – drugs that selectively eliminate senescent cells by inhibiting the pro-survival Senescent Cell Anti-apoptotic Pathways (SCAPs) that protect these cells from apoptosis due to their own SASP. Decreasing senescent cell abundance by intermittent treatment with senolytic drugs decreased frailty in progeroid mice, enhanced cardiac ejection fraction, improved aortic vascular reactivity, and reduced hemeostatic factors in old mice, alleviated impaired gait in mice following leg irradiation, reduced lung fibrosis and enhanced pulmonary function in mice with bleomycin-induced lung dysfunction, reduced insulin resistance in diet-induced obese mice, and decreased vascular calcification, increased vascular reactivity, and decreased atherosclerosis in hypercholesterolemic mice. Thus, senolytic drugs are a new intervention that may delay, prevent, or treat multiple age-and chronic disease-related disorders. Support: NIH grant AG013925, the Connor Group, and the Ted Nash and Glenn Foundations. REFERENCE: Zhu, Y., Tchekonia, T., Pirtskhalava, T., Gower, A., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Borden, G., Lenburg, M., O’Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Straissnigg, H., Gurkar, A.U., Zhao, J., Colangelo, D., Dorrondono, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedenhofer, L.J., Kirkland, J.L. The Achilles’ heel of senescent cells: From transcriptome to senolytic drugs. Aging Cell 14:644-658, 2015.
Results: ALU element content decreased with advancing age ($r = -0.22$; $P < 0.02$) in arteries from melanoma patients. Patients with lower ALU element content had a higher 5-year mortality rate from metastatic disease than those with higher ALU element content (Hazard Ratio (HR) = 4.45; $P < 0.01$). ALU element damage was not correlated with age ($r = 0.14$; $P = 0.10$); but was negatively correlated with ALU element content ($r = -0.32$; $P < 0.01$). Patients with greater amounts of ALU element damage had a higher 5-year mortality rate from metastatic melanoma than those with less ALU element damage (HR = 2.91; $P < 0.04$). Apoptotic signaling was not correlated with age ($r = 0.13$; $P = 0.09$), but demonstrated a positive correlation with ALU element content ($r = 0.25$; $P = 0.01$). Apoptotic signaling was not predictive of mortality from metastatic disease (HR = 0.66; $P = 0.22$).

Conclusions: ALU element instability occurs with advancing age in arteries and is linked to disease progression and lower survival in melanoma patients. DNA damage is associated with age-related ALU element instability and mutant arterial cells may escape apoptosis to promote maladaptive effects in arteries. These findings highlight the relevance of genomic instability in arteries to melanoma pathogenesis.

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12.3 VASCULAR TELOMERE DYSFUNCTION: ASSOCIATION WITH AGING AND FUNCTIONAL IMPLICATIONS
Ashley Walker1

In recent years, the relation between altered telomere function and cardiovascular disease risk has become appreciated. Although epidemiology and physiology studies have typically focused on mean telomere length, there are other features of telomere dysfunction that appear to confer greater physiologic significance, such as the uncapping of telomere ends. Telomeres form specialized structures called t-loops that protect chromosome ends. The loss of this loop, telomere ends. Telomeres form specialized structures called t-loops that protect chromosome ends. The loss of this loop, t-loop that protect chromosome ends. The loss of this loop, known as uncapping, leads to the recognition of telomere ends as double-stranded DNA breaks and initiates a DNA damage response. This DNA damage response causes activation of p53 and p21-mediated cellular senescence. Only a few uncapped telomeres within a cell are needed to trigger a DNA-damage response and telomere uncapping can occur irrespective of changes in mean telomere length.

In human resistance arteries, markers of telomere uncapping and p53/p21-induced senescence increase with advancing age. Importantly, telomere uncapping, but not mean telomere length, is related to markers of cellular senescence in arterial tissue with aging. These age-related changes in telomere uncapping and senescence appear to be greater in women than men, indicating a possible additive effect of menopause and advancing age. To assess the effect that telomere uncapping per se has on vascular function, we utilized a mouse model of induced knockdown of telomeric repeat binding factor 2 (TRF2), a key protein involved in t-loop maintenance. When Trf2 knockout is induced in all cells, there is increased telomere uncapping and p21-mediated senescence in arteries. Whole body Trf2 knockout leads to increased blood pressure and impaired endothelial function, as indicated by reduced endothelium-dependent dilation associated with reduced nitric oxide bioavailability and increased oxidative stress. Knockout of Trf2 induced specifically in endothelial cells also leads to impaired endothelial function characterized by an increase in vascular permeability, indicative of a dysfunctional endothelial barrier.

Thus, advancing age is associated with greater arterial telomere uncapping and cellular senescence. Proof-of-concept studies indicate that induced telomere uncapping can lead to endothelial cell dysfunction. As such, interventions that target the telomere uncapping pathway may be able to prevent or reverse age-related vascular dysfunction and cardiovascular disease risk.

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13.0 POSTER SESSION II

13.1 MYOFILAMENT AND BIOCHEMICAL RESPONSES OF THE RIGHT VENTRICLE TO HYPOXIA-RELATED CARDIAC DYSFUNCTION IN AGING
Danielle Bruns1, Mark Jeong1, Peter Buttrick1, Lori Walker1

Heart failure (HF) is a major public health concern, particularly within aging populations. In age-related left-sided HF as well as other clinical contexts, right ventricular (RV) function is the strongest predictor of survival. However, despite the clear link between RV dysfunction and mortality, little is known about the impact of age on RV function, and no RV-directed therapies exist. Accordingly, the purpose of this investigation was to assess the impact of age on RV function under control conditions and in response to stress using a model of hypobaric hypoxia (HH) (pulmonary hypertension), a highly significant and translationally important disease in cardiovascular aging. We exposed young (3-4 month) and old (~20 months) mice to HH (~17,000 feet; PO2 10%) and assessed myofilament-mediated changes in cardiac contractile function. In HH,
cardiopulmonary morbidity and mortality were significantly accelerated in aged mice, with all HH challenged mice dying within 4 weeks (compared to 0% of young mice). In addition, aged mice exposed to HH had higher lung and RV weights compared to young controls, indicative of more severe pulmonary edema and RV hypertrophy. Assessment of isolated RV cardiomyocyte contractile behavior demonstrated no differences in young versus old control mice. However, cardiomyocytes from old mice exposed to HH demonstrated higher RV myocyte contractile force alongside diminished myofilament cooperativity and a trend towards decreased calcium sensitivity, changes which are directionally similar to those seen in young animals exposed to HH. Since sarcomeric protein biochemistry is a major regulator of the mechanical behavior of cardiac tissue, we quantified phosphorylation of myofilament proteins. Phosphorylation of the inhibitory subunit of the troponin complex (cTnI) was increased at Ser150 in young models of HH exposure and in old RV exposed to HH, albeit less robustly in old animals compared to young. Phosphorylation of cTnI at this site is predominantly modulated by AMP-activated protein kinase (AMPK), which is diminished with aging. AMPK activators are promising targets for HF therapy, thus ongoing investigations will elucidate the impact of AMPK activators on myofilament contractility and cardiac function in the aging and HH-exposed right heart.

13.2 AGING-ASSOCIATED UPREGULATION OF CARDIAC β3-ADRENERGIC SIGNALING IS AN IMPORTANT CAUSE OF CARDIAC AGING

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Aging-Associated Upregulation of Cardiac β3-Adrenergic Signaling is an Important Cause of Cardiac Aging

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Background. Myocardial aging leads to diminished inotropic response to β-adrenergic receptor (AR) stimulation. The molecular mechanism remains unclear. We hypothesize that upregulation of cardiac β3-AR with resultant enhanced negative modulation on β-adrenergic signaling plays a critical role in this age-related event. Thus, aging-induced desensitization of cardiac β-adrenergic signaling may be attenuated or prevented in β3-AR knockout (β3KO) aged mice.

Methods. We compared cardiac β3-AR gene expression and myocyte contractile and [Ca2+]i transient responses to isoproterenol (ISO, 10^-6 to 10^-8 M), a non-selective β agonist, and BRL-37,344 (BRL, 10^-8 M), a selective β3 agonist, in isolated left ventricular (LV) myocytes obtained from 2 young (Y)(~3-4 mo) and 2 aged (A) (~18-24 mo) groups (6/group) of wild-type (WT) and β3KO mice, respectively.

Results. Compared with YWT myocytes, AWT myocytes showed about 30% decline in basal cell contracture (dL/dt_{max}, 86.5 vs 122.1 μm/s) and relaxation (dR/dt_{max}, -61.9 vs -89.9 μm/s) with decreased [Ca2+]i (p<0.01). There were significantly increased β3-AR mRNA (27%, 0.15±0.01 vs 0.12±0.01) and protein levels accompanied by contrast alterations on myocyte response to β- and β3-AR stimulation. In AWT myocytes, ISO (10^-7 M) caused much less increases in dL/dt_{max} (AWT:30% vs YWT:72%), dR/dt_{max} (25% vs 56%), and [Ca2+]i (13% vs 26%); in contrast, BRL produced a much greater decrease in dL/dt_{max} (17.9% vs 6.9%) and [Ca2+]i (28.2% vs 18.7%). Compared with YWT, Yβ3KO, which did not alter basal contraction of myocytes, markedly improved the ISO concentration-response curve. Importantly, in contrast to AWT mice, myocytes obtained from Aβ3KO mice showed significantly improved basal cell contraction and relaxation with nearly preserved ISO-stimulated positive inotropic effect. Compared with Yβ3KO, in Aβ3KO mice, ISO caused similar increases in dL/dt_{max} (78% vs 84%) and [Ca2+]i (32% vs 34%).

Conclusion. Cardiac aging is associated with upregulation of β3-AR, which is a critical determinant to the diminished positive modulation of β-adrenergic signaling, and directly contributes to age-associated deficits in LV myocyte functional performance.

13.3 CARDIAC MYOSIN BINDING PROTEIN-C PHOSPHORYLATION IMPROVES LONGEVITY AND PRESERVES HEART FUNCTION IN AGING HEARTS

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Introduction: In 2014, ≥65Yr population constituted 14.5% (46.2M) of US population. By 2060 this number will double. Heart failure prevalence will increase from 6.5M in 2017 to >8M in 2030 due to the aging population. Cardiac myosin binding protein-C (cMyBP-C), a heart muscle thick filament protein, can regulate cross-bridge attachment/detachment process by its phosphorylation status. cMyBP-C phosphorylation is decreased in heart failure.

Hypothesis: phosphorylated cMyBP-C supports normal heart function during aging.

Results: We test this idea by aging mouse models of phosphorylation deficient cMyBP-C(S273A, S282A, S302A)-(t3SA), phosphorylation mimetic cMyBP-C(S273D, S282D, S302D)-(t3SD), and WT-control cMyBP-C(tWT). t3SD mice showed enhanced survival (Kaplan Meier at 18 months: iWT: 91.8%; t3SA: 89.6%; t3SD: 95.8%, Log Rank test p<0.05). t3SD hearts maintained an EF >45% throughout aging and exhibited enhanced contractility with faster tissue Doppler of myocardial contraction velocity during systole, s'. Conversely, loss of cMyBP-C phosphorylation (t3SA) caused heart failure and systolic...
dysfunction (EF; tWT: 41±4, t3SA: 31±5, t3SD: 48±2), (s1: tWT: 17.05±0.92, t3SA: 15.52±2.09, t3SD: 23.83±1.10). Additionally, t3SD hearts showed enhanced myocardial relaxation velocity during early diastole, e", and smaller blood flow Doppler to e' ratio (E/e'); meanwhile, t3SA hearts exhibited impaired relaxation (s1: tWT: 16.66±1.39, t3SA: 14.04±1.01, t3SD: 33.06±0.01, E/e' in tWT: 34.06±3.99, t3SA: 37.73±2.23, t3SD: 18.49±1.46). We used peak relaxation rate (+dF/dt) to peak force generation rate (+dF/dt max) ratio (dFR) to compare lusitropy of papillary muscles. t3SD muscles show increased dFR, meaning enhanced relaxation (at 1.5 Hz: tWT: 0.56±0.06, t3SA: 0.45±0.02, t3SD: 0.70±0.04). Single negative exponential was used to calculate [Ca2+]i, decay rate constant kc. All models show similar kc; therefore, enhanced relaxation in t3SD is attributed to cross-bridge cycling but not differences in [Ca2+]i handling. Mean±SEM; *p<0.05 vs tWT; #p<0.05 vs t3SD.

Conclusion: Better cardiac function contributed to enhanced survival in t3SD mice. Simultaneous force and [Ca2+]i measurements on papillary muscles showed that t3SD enhancement of relaxation occurs independently of [Ca2+]i. Therefore, acceleration of cross-bridge cycling due to phosphorylation of cMyBP-C can be translated into novel treatments for age-related cardiac dysfunction.

13.4 EARLY CELL-CELL COUPLING IMPAIRS TRANSPLANTED STEM CELL RETENTION AND EFFICACY IN THE ISCHEMIC CARDIOMYOCYTE AND MURINE HEART

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Background: Bone marrow-derived mesenchymal stem cells (BM-MSC) are reported to induce beneficial effects in the heart following ischemia but a loss of these cells within hours of administration could significantly diminish their long-term effect. We hypothesized that early coupling between BM-MSC and ischemic cardiomyocytes through gap junctions (GJ) may play an important role in stem cell survival and retention in the acute phase of myocardial ischemia.

Methods: We seeded HL-1 cardiomyocytes in either normoxic (Nx) or ischemic (Isc) conditions for four hours. Subsequently, murine BM-MSC (mBM-MSC) were seeded on top of the HL-1 monolayer and the co-cultures were returned to incubation under previous conditions (Group 1, Nx, Group 2, Isc) or switched to ischemia-reoxygenation (Group 3, Isc/Nx) for an additional two hours. For the final two-hour co-culture period a GJ inhibitor (Carbenoxolone, CBX: 100 uM) was added to half of the culture plates in each of the three groups. Co-cultures were labeled with Annexin V, Sytox Red, and Sca-1 (mBM-MSC), to identify apoptotic cells and distinguish between HL-1 and mBM-MSC with flow cytometry. To determine the effect of GJ inhibition on mBM-MSC in vivo, we induced ischemia in mice by 90-minute LAD occlusion followed by reperfusion for 24 hours. mBM-MSC, CBX-treated mBM-MSC, or CBX+vehicle alone were injected in the left ventricular apex at the end of the 90 min ischemic period and the mice were allowed to recover. Twenty-four hours after cell injection, left ventricular diastolic and systolic function was assessed by pressure-volume loop analysis with an indwelling LV catheter.

Results: Ischemia induced a greater proportion of dead mBM-MSC in co-culture compared to the Nx group. Isc/Nx resulted in significantly higher early apoptotic but fewer dead mBM-MSC. The presence of the GJ inhibitor CBX in the co-culture reduced the number of dead and apoptotic cells in Isc and Isc/Nx groups by 3-5 fold (p<0.05). Isc/Nx caused impaired cardiac function that was attenuated by mBM-MSC injection. CBX-treated mBM-MSC led to further improvement in cardiac function (mBM-MSC vs. mBM-MSC+CBX: Ees 7.3 ± 1.66 vs. 15.0 ± 5.81; Emax 18.8 ± 6.50 vs. 27.5 ± 9.33; PRSW 49.5 ± 9.89 vs. 99.4 ± 17.4; mean ± SD; p≤0.05; n = 6) while CBX alone did not.

Conclusions: While functional GJ are critical for long-term integration of stem cells within the myocardium, early GJ communication may represent a novel paradigm whereby ischemic and apoptotic cardiomyocytes induce a “bystander effect” when coupled to newly transplanted mBM-MSC and thus impair cell retention and functional benefits.

13.5 DNA-REPAIR IN CARDIOMYOCYTES IS CRITICAL FOR MAINTAINING CARDIAC FUNCTION

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Background: DNA in every cell is continuously damaged and DNA repair systems are essential for protection from DNA damage-induced cancer and aging-related diseases. Here we studied the role of DNA repair in cardiomyocytes in maintaining normal cardiac function. DNA repair-deficient Xpg-/- and cardiomyocyte-specific Xpg-/- (αMHC-Xpg-/-) mice were used to study left ventricular (LV) geometry and function.

Methods: Xpg-/- (n=39), αMHC-Xpg-/- (n=26) and control wildtype (WT, n=28) mice were sacrificed at age 16 wks. LV geometry and function were measured and hypertrophy marker genes were determined. Superoxide (O2-) production was studied using lucigenin-enhanced chemiluminiscence. Molecular imaging was performed to determine early apoptosis in the in vivo heart using near infrared fluorescent Annexin V probe, combined with contrast-enhanced microCT for anatomical reference. Late apoptosis was determined via TUNEL assay in LV sections.

Results: Xpg-/- mice showed reduced growth, followed by body weight loss and shortened lifespan (19 wks). αMHC-Xpg-/- mice exhibited normal growth and body weight gain, but also showed reduced lifespan (28 wks).
16 wks, LV function was deteriorated in both groups compared to WT, demonstrated by decreases in fractional shortening (Xpg−/− 38±2, αMHC-Xpg−/− 28±2 vs. WT 49±2%; both p<0.05) and LVdP/dtmin (Xpg−/− 4020±370, αMHC-Xpg−/− 5380±280 vs. WT 9380±380 mmHg/s; both p<0.05) and increases in relaxation time constant tau (Xpg−/− 10.5±0.7, αMHC-Xpg−/− 11.7±1.5 vs. WT 7.7±0.3 ms; both p<0.05). The relative RNA expression level of atrial natriuretic peptide was increased in both groups, but particularly in αMHC-Xpg−/− (Xpg−/− 3.6±0.3 and αMHC-Xpg−/− 8.6±1.5 fold change; both p<0.05). Total O₂ production was only increased in Xpg−/− (Xpg−/− 49±6, αMHC-Xpg−/− 29±1 vs. WT 26±2 RLU/g; p<0.05). Both Xpg-deficient models displayed marked increases in in vivo myocardial apoptosis (Xpg−/− 3.7±0.9, αMHC-Xpg−/− 2.8±0.3 vs. WT 1.0±0.2 pmol/g heart weight normalized to WT; both p<0.05) as well as in late myocardial apoptosis (Xpg−/− 2.5±0.2, αMHC-Xpg−/− 1.7±0.1 vs. WT 1.0±0.1 positive nuclei % normalized to WT; both p<0.05).

Conclusion: Mice with (cardiomyocyte-restricted) loss of DNA-repair protein XPG display a heart failure phenotype, demonstrating that intact DNA repair in cardiomyocytes is critical for maintaining normal cardiac function.

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13.6 THE EFFECTS OF AGING ON PATHOLOGIC LEFT VENTRICULAR REMODELING AND DYSFUNCTION DEPEND CRITICALLY ON THE UNDERLYING PATHOLOGY

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Purpose: The aging heart undergoes a number of non-pathological structural and functional alterations which are reminiscent to the changes observed in the failing heart, and which thus may increase cardiac vulnerability to develop heart failure in response to mechanical overload. Consequently, we studied the effect of aging on left ventricular (LV) remodeling and dysfunction in response to mechanical overload.

Methods: C57BL/6j mice were subjected to pressure overload by transverse aortic constriction (TAC) or myocardial infarction (MI) at 3 or 24 mo of age. Eight weeks after TAC or MI, LV geometry and function were assessed and isometric force was studied in single permeabilized cardiomyocytes.

Results: Aging resulted in sham-operated animals in increases in LV weight (26%), LV end-diastolic lumen diameter (7%) and passive isometric myofilament force (Fpas, 44%) and in decreases in LVdP/dtmin (22%) and LVdP/dtmax (22%) in 24 vs. 3 mo (all p<0.05). TAC and MI produced LV hypertrophy, LV dysfunction and backward failure in all age groups. Interestingly, the relative TAC- and MI-induced increases in LV weight (compared to age-matched shams) were blunted (TAC: 92% at 3 mo, 60% at 24 mo; MI: 34% at 3 mo, 7% at 24 mo). In TAC, the blunted LV hypertrophy was associated with aggravated LV dysfunction, demonstrated by further decreases in LVdP/dtmin (31%) and LVdP/dtmax (30%) and increases in lung fluid and RV weight (28%) in 24 vs. 3 mo (all p<0.05). In contrast, the blunted MI-induced LV hypertrophy was associated with a trend towards ameliorated LV diastolic dysfunction, demonstrated by reductions in tau (33%) and LV end diastolic pressure (55%) in 24 vs. 3 mo. Furthermore, the survival rate after 8 wk of MI in 24 mo was higher compared to 3 mo (resp. 83% vs. 71%). This was contrary to the survival rate after 8 wk of TAC (70% in 24 mo vs. 88% in 3 mo). The TAC-induced LV dysfunction at 3 mo was accompanied by elevated cardiomyocyte maximal force development (Fmax, 51%), whereas the MI-induced LV dysfunction was accompanied by reduced Fmax (33%), compared to age-matched sham (both p<0.05). Conversely, Fpas was markedly increased in TAC (157%), but unchanged in MI. Aging in TAC resulted in reductions of Fmax and Fpas to baseline sham levels, which were not altered in MI.

Conclusion: These observations indicate that the effects of aging on the cardiac response to hemodynamic overload depend critically on the underlying pathology.

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13.7 ADVANCE AGE AND CIRCULATING MIR423 ARE INDEPENDENT PREDICTORS OF POSTOPERATIVE ATRIAL FIBRILLATION

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Objective: Postoperative atrial fibrillation (PoAF) is a common complication after surgery. Identification of patients at risk of PoAF is difficult in patients undergoing surgery with no prior history of atrial fibrillation (AF) or severe ventricular dysfunction. Circulating miRNAs have been proposed as biomarkers for myocardial dysfunction, but their role in predicting PoAF over clinical predictors is not known. We therefore sought to determine whether miRNA involved in cardiovascular disease can identify those patients who developed PoAF with no prior history of AF and determined the incremental value of miRNA over clinical predictors of AF.

Methods: Preoperative blood from patients undergoing coronary artery bypass graft (CABG) surgery with no previous history of AF, supraventricular or ventricular tachycardia, or severe ventricular dysfunction was used for RNA isolation. Differences in the relative levels of
miRNA between those who did and did not develop PoAF were assessed using qPCR. Area under the curve was used to assess the incremental value of adding miRNAs to clinical predictors on receiver operating characteristics.

Results: Out of 77 patients, 41 developed PoAF (53%). Patients who developed PoAF were older (mean age 69.7± 8.8y vs. 64.4 ±10.2y, p=0.02) and 53% were male; there were no differences in prevalence of hypertension, diabetes, hyperlipidemia, previous myocardial infarction, heart failure, stroke, COPD, sleep apnea, LVEF, or cardiac medications. Out of 12 miRNAs analyzed, only miR423 was significant at the univariate level in predicting patients who developed PoAF [OR 1.12, 95% CL (1.04-1.25), p=0.012]. Multivariate analysis showed that age [OR 1.07, 95% CL (1.01-1.13), p=0.024] and miR423 [OR 1.14, 95% CL (1.04-1.30), p=0.018] were independent predictors of PoAF; male sex, MI, diabetes, CHF, and hypertension were not significantly associated with PoAF (p=0.05). Adding miR423 to clinical predictors improved the C statistics from 0.66 (95% CL 0.54-0.78) to 0.77 (95% CL 0.66-0.88).

Conclusion: In patients undergoing CABG surgery, incorporation of circulating levels of miR423 as a biomarker to clinical predictors improves identification of patients at risk for PoAF and selection for prophylactic intervention to reduce this common complication.

13.8 STORE-OPERATED Ca2+ INFLUX IN HUMAN VENTRICULAR FIBROBLASTS INCREASES BY AGE

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Objective: Senescence-induced changes, including excessive fibrosis, contribute to impaired cardiac function in the elderly. Pro-fibrotic processes like fibroblast (FB) proliferation, activation, secretion of extracellular matrix and cytokines are intracellular Ca2+-dependent. However, the effect of advancing age on the Ca2+ mobilization processes of human ventricular fibroblasts (hVF) is unclear. Therefore, we tested the hypothesis that aging promotes pro-fibrotic changes within hVFs by altering the intracellular Ca2+ release and store-operated Ca2+ influx (SOC).

Methods: Primary hVF cultures, obtained from cardiac disease-free trauma victims of different ages from 2 to 60 years, were used. Cytosolic free Ca2+ imaging was performed in hVF preloaded with fluo-3 AM (confocal microscopy). Thapsigargin (2.5 μM) was used to release and deplete intracellular Ca2+-stores in Ca2+-free KRH solution, and then CaCl2 (2 mM) was added to assess SOC-Ca2+-influx. Ionomycin (2 μM) was used for maximal Ca2+ normalization. Expression of genes related to SOC and fibrosis – STIM1, Orai1, TRPC1, TRPC3, COL1A1, COL1A2, COL3A1, MMP1, MMP2, MMP3, TIMP3 and GAPDH – were assessed by quantitative reverse transcription polymerase chain reaction. Age-related transdifferentiation of hVFs was determined by immunoblotting for α-smooth muscle actin. Collagen secretion/deposition after 48 h culture of hVFs was assayed using a Sircol™ kit. Data were analyzed by age group comparison <50 (n=3-5) vs ≥50 years (3-4) by unpaired Student’s t-test or by regression analysis of the sample population (n=9).

Results: Ca2+ release from intracellular stores by thapsigargin was not different (p=0.12) between <50 (15±1%) and ≥50 groups (24±5%), but SOC-Ca2+-influx was significantly (p=0.04) elevated in the ≥50 group (60±12%) vs the <50 group (32±3%). Regression analysis showed an age-dependent increase in SOC-Ca2+ influx of hVFs (R2=0.5). Age did not significantly alter the expression of genes related to SOC or fibrosis and the status of hVF transdifferentiation to myofibroblasts. The secretion/deposition of soluble collagen by hVFs tends to increase by age (R2=0.4).

Conclusions: Aging-related increase in hVF collagen secretion is associated with increased SOC-Ca2+ influx with no change in the magnitude of intracellular Ca2+ release or the expression of related genes. Regulatory mechanisms that enhance SOC-Ca2+ influx with aging need to be defined to identify specific targets for prevention of excessive fibrosis and myocardial dysfunction in the elderly.

13.9 CARDIAC TROPNIN T AND ENDOTHELIAL CELL DYSFUNCTION IN AGING AND ALZHEIMER’S DISEASE

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Alzheimer’s Disease (AD) is an age-related disorder characterized by progressive cognitive decline and dementia. Growing evidence suggests that the neurodegenerative process is initiated by chronic cerebral hypoperfusion caused by aging related vascular dysfunction. Given that the endothelial cell senescence and apoptosis has severe impact on vascular function in aging, a concerted effort is required to understand the mechanisms underlying vascular endothelial dysfunction in aging and AD to identify novel treatments.

Troponin T (TnT), a key regulator of the muscle contractile machinery, has three isofoms, TnT1, TnT3, and TnT2, which are expressed in slow-, fast-twitch skeletal muscle, and cardiac muscle, respectively. TnT2, or “cardiac” troponin T (cTnT), is also expressed in several noncardiac tissues, including skeletal muscle, smooth muscle and adipose tissue. Its gene expression was also detected in several microvessel endothelial cells from various human tissues, including choroid, retina, and lung. In addition, its protein expression was detected on the surface of cultured primary tumor endothelial cells.

Given that non-myofilament associated cTnT could induce apoptosis in non-muscle cells, we hypothesize that cTnT expression in vascular endothelial cells will increase with aging and AD pathogenesis, which subsequently affects...
endothelium integrity and function. In the current study, using aging and AD mouse models and cultured mouse brain vascular endothelial cells, we reveal (1) cTnT mRNA expression in mouse brain increases with aging and AD pathogenesis; (2) cTnT protein is expressed in brain vascular endothelial cells and its level increases with aging and AD pathogenesis; (3) a higher level of apoptosis exists in the brain of old or AD mice, which is mainly found in cTnT positive cells; and (4) adeno-associated virus serotype 2 (AAV2) is efficient in cultured endothelial cells, while AAV9-mediated cTnT gene expression driven by CMV (universal) or tMCK (skeletal muscle specific) promoter is only successful in cultured C2C12 skeletal muscle cells, but not in cultured brain vascular endothelial cells. Our findings indicate that cTnT may be a potential target to prevent aging and AD associated decline in vascular endothelium function. In addition, AAV2-mediated gene delivery will be an appropriate tool for vascular endothelial cell cTnT targeting.

13.10 SIRT-1 OVEREXPRESSION MITIGATES LARGE ARTERY STIFFENING WITH ADVANCING AGE
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Advancing age is associated with large artery stiffening that is accompanied by lower expression of the cellular deactylase, sirtuin-1 (SIRT-1). Interventions such as lifelong caloric restriction prevent much of the age-related increase in larger artery stiffness while preserving SIRT-1 expression. The aim of this study was to determine if lifelong overexpression of SIRT-1 would attenuate age-related large artery stiffening. Aortic pulse wave velocity (PWV), the gold-standard measurement of large artery stiffness, was measured in SIRT-1 transgenic (SIRTTG) overexpressing and wild-type (WT) littermate control mice developed on a C57BL/6 background. PWV measurements were performed at 3 month intervals from 3-24 months of age. Histological STOC frequency, but not STOC amplitude. Nifedipine-sensitive Ba²⁺ current densities at +30 mV were -0.48 ± 0.6 pA/pF (n=16) in SMCs from Young and were -1 to 1.8 ± 0.6 Hz (n=9, p<0.05) and in Old from 3.5±1 to 1.8±0.5 Hz (n=10, p<0.05). There was no significant effect on STOC amplitude in either age group (p>0.05). Similarly, the CaV1.2 VGCC agonist, BayK8644 (50nM) increased STOC frequency from 6±0.8 to 9.4±1.6 Hz (n=10, p<0.05) in Young and from 5.9±1.4 to 9.8±1.7 Hz (n=10, p<0.05) in Old, again with no effect on STOC amplitude (p>0.05). Thus, Ca²⁺ influx through CaV1.2 VGCCs controls STOC frequency, but not STOC amplitude. Nifedipine-sensitive Ba²⁺ current densities at +30 mV were -0.48±0.3 pA/pF (n=13) in SMCs from Young and -0.85±0.26 pA/pF (n=13) in SMCs from Old (p>0.05 vs. Young). Similarly, BayK8644-stimulated current densities at +30 mV were -3.9±0.6 pA/pF (n=16) in SMCs from Young and were -4.0±0.7 pA/pF (n=16) in SMCs from Old (p<0.05 vs. Young). Our data refute the hypothesis that increased currents through CaV1.2 VGCC account for the increased STOC amplitude that is observed in SEA SMCs from Old. Supported by NIH R01HL086483.

13.12 T CELL DEPLETION IMPROVES ARTERIAL FUNCTION IN BOTH LARGE ELASTIC ARTERIES AND RESISTANCE ARTERIES OF OLD MICE
Aging Enhances Atrial Fibrillation Inducibility in Atherosclerotic Hosts

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Introduction and Rationale: Advanced age is the most critical factor for the development of atrial fibrillation (AF); 10% of patients in their 80s have AF and 50% of patients with AF are 80 years of age or older (Kannel WB et al). Atherosclerosis, a chronic inflammatory condition, is also associated with AF but whether this is due to a direct inflammatory alteration or indirectly via atrial remodeling...
and fibrosis from associated conditions such as hypertension is not known. However, the interplay between aging, atherosclerosis, and AF has not been explored. Here, we examined the effects of a high fat diet (HFD), intended to promote atherosclerosis, and aging on AF inducibility in Ldlr−/− mice.

Methods and Results After programmed electrical stimulation in the right atrium via intravenous catheterization, only 4/10 young (2-4 months of age) chow-fed Ldlr−/− mice exhibited AF, whereas 9/10 young HFD-fed Ldlr−/− mice exhibited AF (Figure 1). Interestingly, 2 of 10 young Ldlr−/− mice fed a HFD exhibited sustained AF (2 hrs), suggesting that a minority of mice fed a HFD for 2 months not only exhibit AF inducibility but sustainability. Under the same protocol, only 1/6 young chow-fed Ldlr−/− mice exhibited AF, in striking contrast to aged (15-16 months of age) chow-fed Ldlr−/− mice that exhibited AF in 4/6 mice (Figure 2). Atrial cardiomyocytes from old, but not young Ldlr−/− mice, exhibited delayed after depolarizations (DADs) and increased propensity for spontaneous calcium release. We next generated bone marrow chimeras of young and aged Ldlr−/− mice by lethally irradiating mice and infusing them with aged-matched or mismatched bone marrow from Ldlr−/− donors, as reported in our prior work (Du W et al). Intriguingly, 3 of 4 young chow-fed Ldlr−/− mice that received aged bone marrow exhibited AF inducibility, whereas transplantation of young bone marrow into aged chow-fed Ldlr−/− mice reduced AF inducibility to 1/6 mice (Figure 2).

Conclusions Atherosclerosis and aging enhance AF inducibility, likely due to hematopoietic factors, in atherosclerotic-prone hosts.


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**Figure 1.** HFD induces AF susceptibility in young Ldlr−/− mice. Young (2 mo of age) Ldlr−/− mice were fed a HFD diet for 2 mo or maintained on a chow diet. At this point mice underwent electrical stimulation of the R atria and surface and intra-atrial ECG were recorded. Bottom: significantly increased AF inducibility in mice on HFD vs Chow.

**Figure 2.** AF incidence is greater in aged than young Ldlr−/− mice, AF incidence is greater in aged than young Ldlr−/− mice, but young mice with old bone marrow have increased AF incidence, whereas old mice with young bone marrow have reduced AF incidence.

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**13.15 MECHANISMS OF IMPAIRED SKELETAL MUSCLE HEMODYNAMICS DURING CONTINUOUS NON-STEADY STATE EXERCISE AND RECOVERY IN AGING HUMANS**

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Blood flow to exercising skeletal muscle is typically reduced with age; however, our understanding of this impairment in humans is largely limited to investigations of steady-state hemodynamics. Here, we continuously measured forearm blood flow (FBF; Doppler ultrasound) and calculated forearm vascular conductance (FVC; FBF/mean arterial pressure) in 14 young (23 ± 1 yrs) and 14 older (67 ± 2 yrs) adults during 3 min of rhythmic handgrip exercise and 2 min of recovery. Subjects performed two randomized, continuous, non-steady state exercise trials: 90 sec at either a low or high workload (10% or 20% of maximum voluntary contraction) followed immediately by transition to the other workload for 90 sec. Thus, subjects completed a low-to-high (L2H) and a high-to-low (H2L) intensity transition. FBF and FVC were quantified in 3 sec bins and cumulative area under the curve (AUC) was calculated throughout. In the L2H trial, vasodilation during the initial workload was reduced ~40% in older compared with young adults (FVC AUC: 72 ± 10 vs. 117 ± 11 ml·100 mmHg−1), and the impairment persisted throughout transition to the high workload (236 ± 30 vs. 373 ± 28 ml·100 mmHg−1) in the H2L trial.
CAD. Ca2+ regulation is pivotal to coronary smooth muscle (MetS), which is associated with a greater risk of developing factors such as unhealthy diet can lead to metabolic syndrome for coronary artery disease (CAD). Other modifiable risk IN, 46202 School of Medicine, 635 Barnhill Dr MS 366, Indianapolis, ml·100 mmHg-1) and recovery (357 ± 43 vs. 557 ± 63 ml·100 mmHg-1; all P<0.05). After 90 sec of exercise, FBF was 30 to 60 ml (L2H and H2L, respectively) lower in older adults and the cumulative age-related deficit increased to ~130 ml by the end of recovery in both trials. In follow-up studies, 2 g of oral ascorbic acid did not improve FBF or FVC in older adults (n=8) during exercise or recovery, and local inhibition of nitric oxide (NO) and prostaglandins (PGs) in young adults (n=12; intra-arterial L-NMMA and ketorolac, respectively) did not affect FBF or FVC beyond the first minute of exercise. We conclude that impaired vasodilation and the magnitude of the blood flow deficit in older adults performing non-steady state exercise increase over time and are not explained by NO or PGs. These findings may have implications for muscle perfusion during activities of daily living in older adults, and the primary mechanisms underlying this age-related impairment remain to be determined.

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13.16 METABOLIC SYNDROME AND ADVANCING AGE ALTER CORONARY SMOOTH MUSCLE CELL CALCIUM HANDLING SIMILARLY IN OSSABAW MINIATURE SWINE
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Introduction: Age is a non-modifiable risk factor for coronary artery disease (CAD). Other modifiable risk factors such unhealthy diet can lead to metabolic syndrome (MetS), which is associated with a greater risk of developing CAD. Ca2+ regulation is pivotal to coronary smooth muscle (CSM) function. Our lab recently found that calcium handling in CSM is dysregulated in CAD in a biphasic manner, with sarcoplasmic reticulum (SR) Ca2+ store increased in early CAD and decreased in late CAD. Aging is associated with increased Ca2+ influx and a greater SR store, similar to Ca2+ handling changes observed in CAD. However, Ca2+ handling in aging and MetS-induced CAD have yet to be compared. Using Ossabaw miniature swine with MetS-induced CAD, we tested the hypothesis that calcium handling in aged lean swine will more closely resemble calcium handling in young swine with MetS vs. young lean swine.

Methods: Young Ossabaw swine (age 2-3.5 years) were placed on either a lean diet or an atherogenic diet. Young swine and aged lean Ossabaw swine (age 7-13 years) were euthanized and coronary arteries were excised from the hearts. CSM cells were enzymatically dispersed from freshly dissected conduit coronary arteries, loaded with the fluorescent [Ca2+], indicator fura-2, and Ca2+ handling studied in a constant-flow superfusion chamber. Membrane depolarization with an 80 mM K+ solution induced Ca2+ influx via voltage-gated calcium channels (VGCCs) and loaded the SR store. Caffeine-induced SR store release and undershoot after removal of caffeine (SR Ca2+ pump [SERCA] activity) were measured. Extrusion by plasmalemmal transporters was determined by examining the time to restore [Ca2+], levels to half of the caffeine-induced peak. VGCC activity was calculated as the slope of Ba2+ influx during superfusion with a 2 mM Ba2+ solution.

Results: Young MetS swine showed significantly higher body weight and cholesterol levels than younger lean swine and aged lean swine, indicating MetS. IVUS analysis also revealed that disease severity was comparable in young MetS swine and aged lean swine. However, young MetS swine showed significantly higher SR store release as compared to young lean controls. This difference was exacerbated in lean aged swine. Aged swine also had significantly attenuated SERCA activity than both young lean swine and young MetS swine, while young MetS swine only trended towards impaired SERCA function when compared to young lean swine. Both young MetS and aged lean swine had significantly higher Ca2+ influx when compared to young lean swine. However, extrusion mechanism function as measured by time to half recovery did not differ between groups.

Conclusion: Overall, aged lean swine show more similar Ca2+ handling to young MetS swine, rather than young lean swine. In fact, many of the Ca2+ handling changes are exacerbated in aged lean swine, indicating that age may be a greater factor in CAD-related Ca2+ handling dysfunction than modifiable cardiometabolic risk factors that give rise to MetS-induced CAD.

13.17 HEALTHY AGING CONVERGES ON A CONSERVED KLF-AUTOPHAGY PATHWAY
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A hallmark of aging is loss of organelle quality control and proteostasis secondary to reduced autophagy. While autophagy, a fundamental mechanism involved in degradation and recycling of dysfunctional cellular components has established pro-longevity effects, our understanding of molecular mechanisms governing autophagy under diverse aging paradigms remains
incompletely understood. Here we show that a family of transcriptional regulators termed Kruppel-like factors (KLFs), are both necessary and sufficient to determine lifespan through control of autophagy in C. elegans and modulate mammalian vascular age-associated phenotypes. Overexpression of C. elegans klf-1 and klf-3 is sufficient to extend lifespan in an autophagy-dependent manner. Additionally, KLFs are necessary for lifespan extension and autophagy across mechanistically distinct longevity models. We further identify a mammalian KLF, KLF4, which also regulates autophagy in mouse embryonic fibroblasts (MEFs), and demonstrate that a KLF4-autophagy pathway may have functional consequences for mammalian longevity. Specifically, increased levels of endothelial restricted KLF4 attenuates age-related loss of vessel compliance, a characteristic age-associated phenotype in mammals, and this effect is dependent on autophagy. Finally, we provide evidence that transcript abundance of KLF4 in human vessels decreases with age. Thus, the KLFs are nodal regulators of autophagic activity and have longevity promoting effects during the aging process.

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13.18 ESTROGEN TREATMENT AND CELLULAR SENESCENCE ON PROTEOSTASIS MAINTENANCE IN ENDOTHELIAL CELLS

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The heat shock response (HSR) is an important cytoprotective mechanism necessary to maintain normal protein homeostasis, and an essential protective response to cellular stress and injury. While a reduction in the HSR in senescent cells has been previously reported, work has been limited to senescent fibroblasts. Given the prevalence of oxidative injury in the aging cardiovascular system, we investigated whether senescent human coronary artery endothelial cells have loss of the HSR and impaired proteostasis, and whether the cytoprotective hormone, 17-beta estradiol (E2), which we previously have found to indirectly increase HSP expression, can mitigate these changes. We found that the senescent (SEN) endothelial cells had a diminished HSR, and also had more protein aggregates than young, early passage (EP) cells. In addition, although E2 treatment did not affect the amount of protein aggregates in either EP or SEN cells, it was able to increase the HSR in EP cells. However, the HSR in senescent cells was unaffected by E2. In sum, aging and senescence in adult human EC is accompanied by a blunting of the HSR and an increase in protein aggregation. E2 did not mitigate these changes in the aging endothelial cells.

13.19 REDUCED GLYCOLYSIS AND INCREASED OXYGEN CONSUMPTION WITH AGING IN ENDOTHELIAL CELLS

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Age-associated vascular endothelial dysfunction is a hallmark of cardiovascular disease (CVD) and is known to be associated with increased arterial oxidative stress. The mitochondria are believed to be an important source of superoxide contributing to age-associated endothelial dysfunction, however the effect of aging on vascular endothelial mitochondrial function per se is not clear. In this present study, we utilized Seahorse™ technology to assess mitochondrial respiration, via changes in the oxygen consumption rate, and glycolysis, via the extracellular acidification rate. We studied cultured primary lung endothelial cells (ECs) from young and old C57BL/6 mice as well as in early (P3) and late (P17) passage human umbilical vein endothelial cells (HUVEC), a cell culture model of aging. We found that old primary ECs demonstrate a 36% higher rate of oxygen consumption (p<0.0001), 11% higher basal respiration (p<0.01), 92% higher proton leak (p<0.0001), and 74% higher spare respiration (p<0.0001) compared with young primary ECs. In contrast, ATP production was 27% (p=0.0001) lower in old compared with young primary ECs. We further demonstrated that mitochondrial extracellular acidification rate is 47% lower (p=0.0001) and maximal glycolytic capacity was 21% lower (p=0.0001) in old compared with young primary ECs. We found similar differences for all variables in late vs. early passage HUVECs as for old vs. young primary ECs. Taken together, our findings suggest that there is a shift in energy production away from glycolysis toward a greater reliance on the mitochondria in old ECs. This higher mitochondrial oxygen consumption in concert with lower rates of ATP production in old ECs may contribute to increased mitochondrial superoxide production and subsequent endothelial dysfunction, a possibility requiring further elucidation.

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Mitochondria have been shown to express a unique nitric oxide (NO) producing nitric oxide synthase (NOS) enzyme named mtNOS. However, the exact pathophysiological role of mtNOS has not been examined. Furthermore, the impact of aging on mtNOS is unclear. The objective of the present study was to examine the impact of aging on the mitochondrial effects of NOS inhibitors. 

Mitochondria from the hearts of young (10 weeks) and middle-aged Sprague Dawley (18 month) rats were isolated by gradient separation. ARL-17477, pharmacological inhibitor of neuronal NOS (1 μmol/L) and NIO, pharmacological inhibitor of eNOS (0.5 μmol/L) were utilized. Mitochondrial oxygen consumption rates by the Seahorse Bioscience Analyzer in isolated cardiac mitochondria were measured in response to ATP synthase inhibitor (Oligomycin, 4 μmol/L), ionophore (FCCP, 4 μmol/L), and electron transport inhibitors (antimycin and rotenone; 8 μmol/L) from old rat hearts showed increased basal respiration (oxygen consumption rate, OCR pmol/min; 95±10 vs 60±12), proton leak (72±24 vs 23±6), decreased maximal respiration (371±54 vs 552±70) accompanied by reduced reserve respiratory capacity (372±50 vs 536±75) compared to that of young rats suggesting increased uncoupling in the aged mitochondria (n=6 pairs of animals each). ARL treatment did not affect mitochondrial basal respiration in both young and aged rats but significantly increased proton leak (110±25 vs 23±6) and decreased ATP production (235±26.5 vs 149±23) in mitochondria only from young rats. ARL treatment tends to correct the decreased maximal respiration (480±55 vs 371±54) and reserve respiratory capacity (451±51 vs 373±50) in mitochondria from aged rats. NIO treatment exerted similar effects as that of ARL, except it increased proton leak from both the young and aged mitochondria. Thus, mtNOS was sensitive to both eNOS and nNOS inhibitors and possibly mediate the transition to aging mitochondrial phenotype. 

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13.21 

ACUTE LYSYL OXIDASE INHIBITION AUGMENTS ENDOTHELIA-DEPENDENT VASODILATION IN YOUNG, BUT NOT MIDDLE-AGED, MEN AND WOMEN.

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The lysyl oxidase family of enzymes (lysyl oxidase (LOX) and the lysyl oxidase-like (LOXL) 1-4 isoforms) catalyzes the formation of collagen cross-linking in the vasculature. LOX is regulated within a narrow physiological window where upregulation of LOX increases vascular stiffness, making LOX a potential molecular target in vascular remodeling, while downregulation of LOX is associated with endothelial dysfunction. In vivo human research on the LOX family is scarce due to the risks associated with prolonged systemic LOX inhibition. The cutaneous microvasculature is a safe and appropriate vascular bed to examine LOX inhibition in vivo due to the localized techniques to facilitate delivery of compounds directly to the skin microvasculature (intradermal microdialysis). Further, age-associated changes in endothelial function are observable in the cutaneous microvasculature and representative of systemic microvascular endothelial dysfunction in both mechanism and magnitude. Our objective was to locally inhibit LOX and LOXL 1-4 in the cutaneous microvasculature to delineate (1) the role of LOX in microvascular endothelial function and (2) age-associated changes in LOX function. Two intradermal microdialysis fibers were placed in the forearm of 10 young (24±1 y) and 10 middle-aged (50±2 y) healthy men and women. Sites were continuously perfused with (1) BAPN to inhibit LOX and LOXL 1-4 and (2) lactated Ringer’s to serve as control; a dose response to the endothelium-dependent agonist acetylcholine (ACh: 10-10-10-1 M) was performed; red cell flux was measured via laser Doppler flowmetry and normalized to cutaneous vascular conductance (CVC: flux×MAP3) and expressed as a percentage of site-specific maximum vasodilation (%CVC max; sodium nitroprusside 50 μM + local heating to 43°C). Data were curve modeled as four parameter logistic regressions and the Log EC50’s compared to determine a change in vasodilator sensitivity. LOX inhibition increased sensitivity to ACh in the young group (LogEC50 ACh: -3.65, ACh + BAPN: -4.34; p=0.03). In contrast, there was no change in sensitivity to ACh in the middle-aged group with BAPN (LogEC50 ACh: -3.41, ACh + BAPN: -3.74; p=0.47). These in vivo human data demonstrate that LOX plays a role in attenuating vasodilator sensitivity to ACh in young men and women, but this effect is lost by middle age. This suggests that the LOX family of enzymes play a functional role in the cutaneous microvasculature and that the actions of LOX are age-dependent.

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13.22 

THE EFFECTS OF TWO WEEKS OF REDUCED DAILY ACTIVITY ON THE SKELETAL MUSCLE MICROVASCULAR FUNCTION OF ELDERLY MEN

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The prolonged lack of physical activity in elderly adults increases the risk for the development of chronic metabolic diseases including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Even short-term periods of inactivity can significantly impair glycemic regulation and cause obvious muscle loss (sarcopenia). It is now apparent that the skeletal muscle microvasculature plays a critical role in establishing insulin sensitivity by controlling both delivery and access of insulin and glucose to the musculature, however, the effect of these periods of inactivity on skeletal muscle capillary recruitment is relatively unknown. The purpose of the present study was to determine...
ARTERIES IN AGED SKELETAL MUSCLE RESISTANCE
VASCULAR SMOOTH MUSCLE CONTRACTILITY
EFFECT OF INTRALUMINAL PRESSURE ON
VASCULAR SMOOTH MUSCLE CONTRACTILITY
IN AGED SKELETAL MUSCLE RESISTANCE ARTERIES
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Objective: We tested the hypothesis that exposure to an acute increase in intraluminal pressure improves vascular smooth muscle (VSM) contractility in aged skeletal muscle resistance arteries.

Methods: Soleus muscle feed arteries (SFA) from young (4 mo) and old (24 mo) Fischer 344 rats were cannulated with microtip perfusion catheters and endothelial cells were removed (denuded) by passing 5 ml of air through the lumen of the vessel. SFA were then pressurized to 90 cmH2O for 1 h. At the end of the 1-h treatment, intraluminal pressure in all arteries was set to 90 cmH2O for examination of VSM contractile function. Contractile responses were assessed using increasing whole log doses of norepinephrine (NE; 10^-6-10^-7 M), angiotensin II (Ang II; 10^-7-10^-8 M), and phenylephrine (PE; 10^-4-10^-6 M). To assess the role of the RhoA pathway, VSM constrictor responses were assessed in the absence or presence of a RhoA-kinase inhibitor (Y27632; 10^-6 M).

Results: Constrictor responses of denuded SFA to PE and Ang II were significantly impaired in Old SFA relative to young SFA, whereas constrictor responses to NE were preserved. In the presence of Y27632, to inhibit Rho Kinase, constrictor responses to Ang II, and PE were significantly blunted in young and old denuded SFA. In addition, the age-group difference in constrictor responses to Ang II was eliminated. Treatment of old SFA with an acute (1 h) increase in intraluminal pressure resulted in impaired (not improved) VSM constrictor responses to NE, PE and Ang II.

Conclusion: The results of this study indicate that VSM contractile function declines with age due, in part, to impaired RhoA-signaling. Contrary to our hypothesis, treatment with an acute increase in intraluminal pressure did not improve VSM contractile function in aged SFA.

SIRT1 NEGATIVELY REGULATES INFLAMMATION AND AGING-INDUCED ENDOTHELIAL BARRIER DYSFUNCTION
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Aging is a major risk factor for endothelial barrier dysfunction and vascular hyperpermeability, which contributes to the development and progression of cardiovascular disease. Aging is associated with chronic low-grade systemic inflammation and inflammatory signaling leads to increased endothelial barrier permeability. Sirtuins, NAD-dependent deacetylases, are tightly associated with aging and longevity from yeast to mammals. Deletion of Sirtuin 1 (Sirt1) results in upregulation of acetylated NFκB and increased inflammatory responses, while SIRT1 activators reverse age-related vascular endothelial dysfunction and inflammation. Despite an established relation between SIRT1 and vascular aging, how sirtuins regulate endothelial barrier function is poorly understood. To study the role of sirtuins in endothelial permeability with aging, we examined primary mouse lung endothelial cells (MLECs) isolated from young (4-6 months) and old (24 months) SIRT1

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transgenic overexpressing (SIRT1\textsuperscript{TG}) and wildtype (WT) littermate mice with electric cell-substrate impedance sensing (ECIS), an in vitro continuous monitoring system that quantifies attachment and spreading of cells. In WT mice, MLECs from old mice were 80% more permeable than MLECs from young mice (p<0.0001); Whereas MLECs from young SIRT1\textsuperscript{TG} mice were 18% less permeable than MLECs from age-matched WT mice (p<0.005). To examine the impact of aging and SIRT1 overexpression on the cytokine-induced impairments in barrier function, MLECs were incubated with TNFa (2ng/ml; 20 hrs) or IL-1\beta (10ng/ml; 40 hrs). TNFa-induced permeability was 5% greater in MLECs from old compared with young mice (p<0.001). SIRT1 overexpression appears to protect against the age-associated increase in cytokine-induced endothelial permeability, as IL-1\beta induced EC permeability was 47% lower in MLECs from young SIRT1\textsuperscript{TG} mice compared with age-matched WT mice (p<0.001). To further confirm the role of Sirt1 in regulation of endothelial barrier function, MLECs from young WT mice were treated with the NAD\(^+\) precursor, nicotinamide mononucleotide (NMN), a Sirt1 activator. NMN treatment inhibited IL-1\beta induced EC permeability by 30% (p<0.0001). Our findings suggest that Sirt1 protects against age-related endothelial cell barrier dysfunction at baseline and in response to inflammatory stimuli.

13.25

ENDOTHELIAL CELL AUTOPHAGY MAINTAINS SHEAR-STRESS-INDUCED NITRIC OXIDE GENERATION VIA GLYCOLYSIS-DEPENDENT PURINERGIC SIGNALING TO ENOS

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Endothelial cell autophagy and nitric oxide (NO) generation are compromised by aging but a mechanistic link has not been defined. Earlier we reported that genetic and pharmacological approaches that limit autophagy in bovine arterial endothelial cells (ECs) prevent shear-stress induced p-eNOS\textsuperscript{1177} and NO production. We sought to determine the responsible mechanism. Upon autophagy compromise in ECs exposed to shear-stress, impaired EC glucose uptake and EC glycolysis attenuated ATP production. We hypothesized that decreased glycolysis-dependent purinergic signaling via P2Y\(_1\) receptors prevents shear-induced NO generation. Manoeuvres that restore glucose transport and glycolysis (e.g. overexpression of GLUT1) or purinergic signaling (e.g. addition of exogenous ADP) rescue shear-induced p-eNOS\textsuperscript{1177} and NO production in ECs with impaired autophagy. Conversely, GLUT1 siRNA, impairing purinergic signaling via ectonucleotidase-mediated ATP/ADP degradation (e.g. apyrase), or by pharmacological (e.g. MRS2179) or genetic (e.g. P2Y1-R siRNA) inhibition of P2Y\(_1\) receptors, inhibits shear-induced p-eNOS\textsuperscript{1177} and NO generation in ECs with intact autophagy. Supporting a central role for PKC\(_\delta\) in relaying the autophagy-dependent purinergic-mediated signal to eNOS, we find that: (i) shear-stress induced activating phosphorylation of PKC\(_\delta\)\textsuperscript{T505} is negated by inhibiting autophagy; (ii) shear-induced p-eNOS\textsuperscript{1177} and NO generation are restored in autophagy-impaired ECs via pharmacological (e.g. bryostatin) or genetic (e.g. CA-PKC\(_\delta\)) activation of PKC\(_\delta\)\textsuperscript{T505}; and (iii) pharmacological (e.g. rotterlin) and genetic (e.g. PKC\(_\delta\) siRNA) PKC\(_\delta\) inhibition prevents shear-induced p-eNOS\textsuperscript{1177} and NO generation in ECs with intact autophagy. Importantly, key nodes in this signaling pathway are recapitulated in human arterial endothelial cells with suppressed autophagy, and in mice with temporal deletion of Atg3 specifically in ECs. Targeted reactivation of purinergic signaling and/or PKC\(_\delta\) has strategic potential to restore compromised EC NO generation in the context of aging-associated autophagy suppression.

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13.26

ROLE OF DAMPS IN DEVELOPMENT OF MICROVASCULAR DYSFUNCTION IN HUMAN CORONARY ARTERY DISEASE

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BACKGROUND: Despite decades of intense research, cardiovascular diseases associated with aging remain the leading cause of death in the western world. Microvascular endothelial dysfunction is an early indicator of future adverse cardiac events, even before onset of large vessel damage. We have shown that in subjects with coronary artery disease (CAD), microvascular flow-mediated dilation (FMD) switches from a NO-mediated to a H\(_2\)O\(_2\)-mediated mechanism with corresponding elevations in mitochondrial reactive oxygen species (mtROS). Interestingly, patients with CAD display increased mitochondrial DNA (mtDNA) damage. We hypothesized that increased levels of circulating mtDNA fragments, termed Damage Associated Molecular Patterns (mtDAMPs), are responsible for the endothelial dysfunction in CAD by activating Toll Like Receptor 9 (TLR9), increasing ROS formation, and decreasing NO production.

METHODS: We examined the effect of increased mtDAMPs on the mechanism of FMD in isolated human microvessels (~200µm) from patients without CAD. We also evaluated H\(_2\)O\(_2\) levels (Amplex red) and eNOS (Nitrlic Oxide Synthase) expression in cultured endothelial cells (EC) after exposure to mtDAMPs or a TLR9 agonist. Finally, Mitochondria2 mice (mitochondria-localized fluorescent protein) were used to evaluate endothelial mitochondrial fission/fusion.

RESULTS: Exposure to mtDAMPs switched the mechanism of FMD from NO to H\(_2\)O\(_2\) in non-CAD vessels
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(% Max Diameter: Control 84.7±8.2; + L-NAME: 89.4±5.5; + Peg-Cat 35.4±10.8; N=3), increased H2O2 production; and decreased eNOS phosphorylation (Ratio Phospho/Total eNOS: Vehicle 1.60±0.27 vs. mtDAMPs: 0.04±0.004, N=4). Similar patterns were observed following treatment with a TLR9 agonist. mtDAMPs promoted mitochondrial fission (Mitochondrial Fragmentation Count: mtDAMPs 21.67 ± 1.31 vs. vehicle 9.8 ± 0.4; p<0.0001; Form Factor/Aspect Ratio: mtDAMPs 1.62 ± 0.04/1.77±0.02 vs. Vehicle 2.55 ± 0.08/2.54 ± 0.06; p<0.0001) compared to the vehicle.

CONCLUSION: Our data suggest that mtDAMPs increase mitochondrial fission, increase H2O2 levels, and shift the mechanism of FMD from NO - to H2O2-dependent. We conclude that elevated mtDAMPs are sufficient to produce a microvascular CAD phenotypic.

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13.27 BLOOD PRESSURE IN ELDERLY KIDNEY TRANSPLANT RECIPIENTS
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Background: Hypertension is a high prevalence in elderly. The association between age and hypertension after kidney transplantation and pattern of blood pressure in elderly kidney transplant recipients are unclear.

Methods: This is a retrospective, closed cohort study conducted in kidney transplantation recipients during 12-month period. A total of 70 patients were divided into 2 age groups: < 60 and ≥60 years old. Post-transplant hypertension is defined by systolic or diastolic blood pressure (SBP or DBP) ≥140 or 90 mmHg, respectively.

Results: Of all 70 patients, mean age±SEM was 52.66±1.43 years. The majority of the patients were male (41 patients, 58.6%). Since there are many variability in blood pressure measurement during early post-transplant period, blood pressure was started reviewed from 4 weeks post-transplant and then at 12, 24, 36, and 48 weeks post-transplantation. Relative risk was used to measure the association between the patients’ age and hypertension (Table 1). Older age group appears to have greater risk of systolic hypertension then younger age group (except at 4 weeks post-transplantation); whereas, they had lower risk for diastolic hypertension. Although, the elderly-hypertension association during different time post-transplant were not statistically significant, the association of elderly and post-transplant hypertension both systolic and diastolic were significant at 24 weeks post-transplantation as well as systolic hypertension at 36 weeks post-transplantation. By using heterogeneity effects method, body mass index (BMI) is a potential effect measure modification between old age and post-transplant hypertension.

Conclusion: Compared to younger age kidney transplant recipients, older age patients are at higher risk for systolic hypertension and appear to have lower DBP. This pattern seems to be similar to non-transplant elderly patients.

Table 1: Association between 2 different patient groups stratified by age and hypertension.

| BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; RR, relative risk; SBP, systolic blood pressure |
|---|---|---|---|---|
| **BMI** | SBP | DBP |
| (under 25) | (25-29.9) | (≥30) | (under 25) | (25-29.9) | (≥30) |
| 14 | 0.875 | 0.598-1.922 | 0.787 | 0.156 | 0.023-1.109 | 0.27 |
| 12 | 1.286 | 0.681-2.428 | 0.587 | 0.381 | 0.093-1.555 | 0.190 |
| 44 | 1.905 | 1.107-3.260 | 0.640 | 2.690 | 1.697-4.320 | 0 |

14.0 SYMPOSIUM: MITOCHONDRIA: THE EPICENTER OF AGING RELATED CARDIOVASCULAR DEFECTS

14.1 THE REQUISITE ROLE OF MITOCHONDRIA IN INTERACTIONS BETWEEN CARDIAC MYOCYTES AND THE CORONARY VASCULATURE
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Mitochondrial dysfunction in obesity and diabetes can be caused by excessive production of free radicals, which can damage mitochondrial DNA. Because mitochondrial DNA plays a key role in the production of ATP necessary for cardiac work, we hypothesized that mitochondrial dysfunction, induced by mitochondrial DNA damage, uncouples coronary blood flow from cardiac work. Myocardial blood flow (contrast echocardiography) was measured in Zucker lean (ZLN) and obese fatty (ZOF) rats during increased cardiac metabolism (product of heart rate and arterial pressure, i.e. norepinephrine). In ZLN increased metabolism augmented coronary blood flow, but in ZOF metabolic hyperemia was attenuated. Mitochondrial respiration was impaired and ROS production was greater in ZOF than ZLN. These were associated with mitochondrial DNA (mtDNA) damage in ZOF. To determine if coronary metabolic dilation, the hyperemic response induced by heightened cardiac metabolism, is linked to mitochondrial function we introduced recombinant proteins (intravenously or intraperitoneally) in ZLN and ZOF to fragment or repair mtDNA, respectively. Repair of mtDNA damage restored mitochondrial function and metabolic dilation, and reduced ROS production in ZOF; whereas induction of mtDNA damage in ZLN reduced mitochondrial function, increased ROS production, and attenuated metabolic dilation. Adequate metabolic dilation was also associated with the extracellular release of ADP, ATP, and H₂O₂ by cardiac myocytes; whereas myocytes from rats with impaired dilation released only H₂O₂. Mitochondrial function plays a seminal role in connecting myocardial blood flow to metabolism, and integrity of mtDNA is central to this process.

14.4
NON CANONICAL TELOMERASE AS REGULATOR OF MITOCOCHONDRIAL HEALTH AND ENDOTHELIAL FUNCTION
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The catalytic subunit of the Telomerase holoenzyme, TERT, counteracts telomere shortening. Recently a non-canonical role in attenuating formation of mitochondrial reactive oxygen species (mtROS) in coronary arterioles from subjects with coronary artery disease (CAD) has been identified. We demonstrated that activation of TERT can reverse the mechanism of flow-induced endothelium-dependent dilation (FMD) from H₂O₂- to NO, restoring the phenotype to one observed in subjects without CAD. mtROS is known to promote development of arteriosclerosis and endothelial dysfunction, predisposing individuals to vascular complications. NO has a well-known inhibitory effect on mtROS generation and has also been demonstrated to increase telomerase.

The underlying mechanism how mitochondrial TERT asserts its protective effects are not known. We have observed that the dominant negative splice variant β del TERT is elevated in subjects with CAD, while overall amounts of TERT are decreased. β del TERT elevates mitochondrial DNA damage leading to an increase in ROS production.

Telomerase is also known to be a key factor in initiation of autophagy, a critical regulator of cellular homeostasis via recycling damaged proteins and organelles. Decreased telomerase levels are known to impair autophagy resulting in decreased stress response and elevated ROS levels.

During pathological stress elevated levels of ROS can attenuate endothelial function and shear-induced NO formation. Superoxide is also produced with physiological stimuli (e.g. shear) but any damaging effects are held in check by endogenous cellular systems including autophagy. Autophagic flux is necessary for shear-induced release of NO in isolated human microvessels while mal-adapted autophagy results in excess oxidative stress and greater susceptibility to oxidant-induced injury. Whether nuclear or mitochondrial telomerase activity contributes to these changes is not established. We developed novel decoy peptide that prevent nuclear (nucXTERT) or mitochondrial (mitoXTERT) translocation of TERT allowing us to differentiate the roles of nuclear and mitochondrial telomerase in mediating vascular protective phenotypes.

We hypothesize that mitochondrial telomerase plays a protective role by preventing mtDNA damage in normal conditions and promoting autophagy. Expression of β del TERT in disease suppresses this protective effect and elevates vascular cellular oxidative stress to induce the conversion from NO to H₂O₂ as the mediator of FMD.

LATENESS REPORT ABSTRACTS

LB001
EXERCISE PREVENTS CARDIOMETABOLIC DYSFUNCTIONS IN ANGIOTENSIN II-INDUCED RAT MODELS OF METABOLIC SYNDROME
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Background: Skeletal muscle insulin resistance frequently occurs with glucose intolerance, hyperinsulinemia, dyslipidemia, essential hypertension, and central obesity. These metabolic and cardiovascular abnormalities are known as insulin resistance syndrome, a major risk factor of diabetes and cardiovascular diseases. Angiotensin II (ANGII) is a potent vasoactive peptide that has been demonstrated to be one of the causes of insulin resistance condition. Multiple cardiometabolic abnormalities including hypertension, dyslipidemia, and impaired insulin sensitivity developed in rats that infused with ANGII. Even though physical exercise is known to attenuate risks of cardiovascular diseases in humans and animals that consumed high-calorie diet, it remains to be elucidated whether exercise could relieve cardiometabolic conditions induced by chronic ANGII infusion.

Objectives: This study assessed the protective effects of physical exercise by voluntary wheel running (VWR) in ANGII-infused rats.

Methods: Adult male Sprague-Dawley rats were randomly assigned to sedentary or VWR groups. After a 6-
wk period of sedentary or VWR, rats in each group were subdivided and subcutaneously administered with either normal saline or ANGII (100 ng/kg/min) for 14 days. Following 10 days, an oral glucose tolerance test was performed to determine whole body insulin sensitivity. 4 days later, animals were terminated and skeletal muscle glucose transport activity were measured in isolated soleus muscles.

**Results:** We found that VWR decreased body weight, fat weight, and systolic blood pressure as well as improved serum lipid profiles in ANGII-infused rats. Moreover, insulin resistance of glucose transport and impaired insulin signaling molecules were not observed in the soleus muscle of ANGII-infused rats that underwent VWR. The soleus muscle of VWR rats was associated with significant increases in GLUT-4 protein abundance (109%) and the level of AMPK Thr172 (43%) and decreases in oxidative stress marker (31%) and the levels of insulin-induced p38 MAPK Thr180/Tyr182 (45%) and SAPK/JNK Thr183/Tyr185 (25%).

**Conclusions:** The present investigation demonstrated that prior voluntary exercise could prevent the progression of cardiometabolic syndrome in insulin-resistant rats induced by chronic ANGII administration as well as improve cardiometabolic profile in rats with normal insulin sensitivity.

This work was supported by grants from The Thailand Research Fund (TRF) through the Royal Golden Jubilee (RGGJ) Ph.D. Program (Grant PHD/0228/2552)

**LB002**

**ROLE OF VASCULAR AGING IN LUNG REGENERATION**

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Aging is associated with impaired organ function and increased susceptibility to various chronic diseases, including chronic obstructive pulmonary disease (COPD). Impairment of lung regeneration and repair contributes to the pathogenesis of COPD. While compensatory lung growth after pneumonectomy (PNX) is highly induced in lungs of juvenile people, aging reduces the regenerative ability in insulin-resistant rats induced by chronic ANGII administration as well as improve cardiometabolic profile in rats with normal insulin sensitivity.

This work was supported by grants from The Thailand Research Fund (TRF) through the Royal Golden Jubilee (RGGJ) Ph.D. Program (Grant PHD/0228/2552)

**LB003**

**HIGHER PLASMA CONCENTRATIONS OF THE GUT-DERIVED METABOLITE TRIMETHYLAMINE N-OXIDE IS CORRELATED WITH IMPAIRED ARTERIAL AND COGNITIVE FUNCTION IN YOUNG AND OLDER HEALTHY ADULTS**

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Aging is associated with impaired arterial endothelial function and stiffening of the large elastic arteries, which contribute to the development of other age-related disorders, including impaired cognitive function. One underlying cause of this impaired arterial function may be age-related alterations in the gut microbiome, including increased production of adverse gut-derived metabolites, such as trimethylamine N-oxide (TMAO). Elevated TMAO has been linked to atherosclerosis and Alzheimer’s disease; however, whether TMAO contributes to impairments in function that precede clinical disease is unknown.

**PURPOSE:** We sought to determine if plasma TMAO increases with aging in humans and if such increases in circulating TMAO are related to impaired arterial and/or cognitive function. **METHODS:** Plasma was collected from healthy young (N=12; 22±1yr) and middle-aged to older (MA/O; N=49; 65±7yr) adults who also underwent baseline arterial testing to assess endothelial function (brachial artery flow-mediated dilation, FMD) and arterial stiffness (carotid-femoral pulse wave velocity, PWVc-f). Cognitive function was assessed in a subset of MA/O adults (N=36) using the NIH Toolbox. Relations between plasma [TMAO], analyzed using liquid chromatography-mass spectrometry, and arterial and cognitive function outcomes were determined using linear regression models, unadjusted and adjusted for cardiovascular (CV) risk factors. **RESULTS:** Compared to young adults, plasma [TMAO] was ~4-fold higher in MA/O adults (4.8±2.3 vs. 1.1±0.4 μM, p<0.001), FMD was ~50% lower (4.1±2.1 vs. 8.3±2.4%, p<0.001), and PWV was ~40% higher (857±182 vs. 611±49 cm/sec, p<0.001). In unadjusted models, higher plasma [TMAO] was related (inversely) to FMD (r2=−0.29, p<0.001) and (positively) to PWVc-f (r2=0.13, p<0.03). These relations remained, and were actually strengthened, when controlling for age, cardiorespiratory fitness (VO2max), body mass index, and serum low-density lipoprotein cholesterol (FMD: r2=0.36, p=0.001; PWVc-f: r2=0.37, p=0.01). Higher plasma [TMAO] was also related (inversely) to Fluid Cognition Composite
Score, which includes measures of executive function, episodic and working memory, and processing speed (unadjusted: $r^2=0.13$, $p=0.03$; adjusted for CV risk factors: $r^2=0.30$, $p=0.049$). CONCLUSIONS: Circulating levels of TMAO are increased in MA/O adults and are related to impaired endothelial function, arterial stiffness, and impaired cognitive function.

Supported by R01 HL134887

**LB004**

**AGE AND TIME DEPENDENCE OF POST-OVARIECTOMY ESTRADIOL TREATMENT ON CARDIOVASCULAR REGULATION IN DAHL SALT-SENSITIVE RATS**

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**Objective:** To assess the mechanisms for differences in regulation of the cardiovascular system of Dahl salt-sensitive (DS) rats to estradiol (E2) treatment as a function of time following ovariectomy as a model for women who initiate E2 replacement therapy post-menopausally or post-oophorectomy.

**Methods:** DS rats were ovariectomized (OVX) at 4.5 mo (DS-OVX$^4$) or 7 mo of age (DS-OVX$^5$). At 7 mo, OVX DS rats in each group were treated with E2 for 4 weeks (DS-OVX$^4$E2, DS-OVX$^5$E2) or vehicle. Mean arterial blood pressure (MAP) was measured telemetrically in all groups from 7-8 mo. Body weight (BW) was measured throughout the experiment and plasma angiotensin II (AngII) concentration was measured at time of sacrifice (8mo) by RAS-Fingerprint$^TM$ (Attoquant). Brain morphometric and receptor autoradiographic determinations of angiotensin II receptor determinations are in process.

**Results:** As reported concurrently (Council for High Blood Pressure, 2017), E2 treatment at 7 mo did not alter MAP in DS-OVX$^5$, but it did prevent the ovariectomy-induced increase in MAP in the DS-OVX$^4$. E2 treatment reduced BW in both the DS-OVX$^4$ and the DS-OVX$^5$ groups. E2 treatment reduced plasma AngII in both DS-OVX$^4$ and DS-OVX$^5$ groups by $\sim$40% compared to their vehicle-treated controls. Brain AT1 angiotensin receptor expression has been shown to be reduced in the solitary tract nucleus of OVX-DS versus SHAM-DS rats (Society for Neuroscience, 2017) and assays are in process to determine if E2 treatment will alter this change. Additionally, the ventricles of the DS rats tend to be enlarged compared to other rat strains suggestive of disturbed fluid balance in the DS female brain.

**Conclusions:** E2 replacement attenuates the increase in MAP in 7 mo old DS rats when treatment begins immediately post-ovariectomy, but not when initiated 3.5 mo post-OVX in young DS rats. The E2-induced change in BW and plasma AngII concentration did not differ with time of initiation of treatment post-ovariectomy, suggesting that changes in brain Ang II receptor expression may explain the differential blood pressure responses. These findings are relevant to treatment of ovarian hormone-deficient women with E2. Funding sources: NIH HL- 121456 and Peptide Radiotiodination Shared Resource, Georgetown University.

**LB005**

**O$_2$ AVAILABILITY AND METABOLIC RESERVE: EVIDENCE OF DIFFERENT SKELETAL MUSCLE PHENOTYPES IN COPD**

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Exertional dyspnea and exercise intolerance are hallmark manifestations of chronic obstructive pulmonary disease (COPD). However, despite the debilitating consequences of the disease, the pathophysiological mechanisms that underpin the loss of exercise capacity and mobility in patients with COPD are still unclear. Overall, the literature suggest that patients with COPD exhibit anomalies of both peripheral O$_2$ transport and muscle bioenergetics which have the potential to limit exercise capacity. However, their actual contribution to exercise intolerance is still debated, likely in part, due the pathophysiological heterogeneity of COPD. Therefore, the purpose of this study was to determine the physiological determinants of muscle aerobic capacity in COPD patients. Specifically, we examined whether a brief ischemia during exercise followed by reactive hyperemia (RH) would affect peripheral O$_2$ supply and mitochondrial function in patients with COPD. 18 patients with moderate to severe COPD performed plantar flexion exercise while phosphorus magnetic resonance spectroscopy, near-infrared spectroscopy, and Doppler ultrasound were used to assess muscle metabolism and peripheral hemodynamics. In 8 subjects, “responders”, convective (free-flow area under the curve, AUC FF: 0.18±0.15 L.min$^{-1}$; RH: 0.34±0.20 L.min$^{-1}$) and diffusive O$_2$ delivery were significantly increased in RH, resulting in significantly higher mitochondrial phosphorylation capacity (FF: 18±8 mM.min$^{-1}$; RH: 31±9 mM.min$^{-1}$). In 10 subjects, “non-responders”, neither convective (AUC FF: 0.23±0.10 L.min$^{-1}$; RH: 0.32±0.09 L.min$^{-1}$) and diffusive O$_2$ delivery, nor mitochondrial phosphorylation capacity (FF: 29±12 mM.min$^{-1}$; RH: 23±7 mM.min$^{-1}$) were significantly different.
between conditions. In conclusion, the current integrative study revealed two subgroups of COPD patients with different muscle phenotypes. Nearly half of the patients with COPD appeared to exhibit a metabolic reserve in the plantar flexor muscles whereas the other half demonstrated a loss of convective and diffusive O₂ delivery reserve, potentially combined with intrinsic limitation of the mitochondrial capacity to synthesize ATP. Together, our findings clearly highlight the importance of identifying the different phenotypes within the wide spectrum of COPD when exploring the effectiveness of novel therapeutic treatments.
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